NEW CHS RESOURCE AVAILABLE FOR FAMILIES

All About Hemophilia: A Guide for Families will be available at Hemophilia Treatment Centres in December, 2001. The French version will be available in the new year. This comprehensive new resource includes both detailed medical information and the stories of children and families living with hemophilia.

More details on p22
As we approach the holiday season and prepare to celebrate a promise of peace and joy throughout the world (wouldn’t it be marvellous if it could actually happen?), it is wise to reflect on the successes and promises the past years of work on hemophilia issues have provided us. This issue of Hemophilia Today is full of such information. But three areas stand out as deserving particular attention from your Editor.

The first is the matter of research into hemophilia concerns, both medical and psycho-social. And the amount of research that is being conducted into hemophilia matters is, frankly, enormous, as the number of articles on Canadian research alone in this issue attests. We ought to be both encouraged and proud of our endeavours, as much of this research is a direct result of funding provided by our Hemophilia Research Fund. And most of those funds have been generated within the hemophilia community by the Million Dollar Club. We ought also to thank our partners in industry who have been generous in their funding of various research programs.

The second matter that strikes your Editor as being of particular interest is the establishment of “twinned” hemophilia centres. Eric Stolte reports on his findings from a trip to Mongolia where another hemophilia clinic is being twinned with a Canadian centre, specifically the Saskatoon Hemophilia Clinic. His report on the condition of Mongolian hemophiliacs and their treatment is both fascinating and heart-wrenching. If any one of us ever feels as though our health care is being overlooked or ignored in any way, he ought to read Eric’s article and be generally content with the state of care in Canada. (That does NOT mean that we ought to let our health care systems be eroded away by constant governmental under-funding.)

The promise that this generous gesture offers to Mongolian hemophiliacs is enormous. With each such twinning project the CHS continues to support third world nations as they begin to offer modern medicine to their citizens.

The third area that strikes your Editor as being worthy of special mention is the production of “All About Hemophilia: A Guide for Families,” one of whose authors is Karen Creighton, a mother of three boys with hemophilia. Karen reports on the work that has gone into this publication in her column, “Families In Touch.” This new information package is huge, written by over 25 authors, consisting of some 300 pages. It is a complete revision of our resource guide, “Hemophilia in Perspective,” originally published in 1993. The editor of this new publication, David Page, ought to be proud, and so too should all the contributors to “All About Hemophilia: A Guide to Families.” Congratulations on a job well done.

As a Society that believes in helping to provide the best medical care possible to its members, and believes that the publication of information is a major part of that provision, the CHS and its members ought to be proud of the advances that are being made, because those advances are being funded, in part at least, by our own members, and the advances in care are being made available in preliminary ways beyond our borders. We ought to be proud of the many successes and promises our efforts have given us. We ought to be able to feel good about the holiday season that is swiftly approaching, a season whose very core is promise.

[Please feel free to respond to this Editorial or to any other material that has appeared in Hemophilia Today by writing to The Editor, Hemophilia Today, 1409B 4th Street, N.W., Calgary, Alberta T2M 2Y8, or by fax at (403) 282-3295, or by e-mail at bisac@cadvision.com.]
CHS—Supporting New Research

In this column, I will review the ways in which the CHS encourages and supports research. Research that is aimed either at finding cures or improving the care available to people with bleeding disorders requires two things: highly qualified researchers who are interested in doing the work and money in the form of research grants to support their research projects. Both these necessary commodities are in short supply.

The number of physicians interested in treating or doing research on bleeding disorders is small. One reason for the small number of interested physicians is that all the inherited bleeding disorders except von Willebrand Disease (VWD) disease are quite rare. And although VWD is more common than some disorders (e.g., AIDS or multiple sclerosis) that command the attention of large numbers of treaters and researchers, VWD is not a “fashionable” disease that has attracted much attention. In addition, many of our current treaters and researchers are nearing retirement. Taken together, these facts mean that we are facing a worsening shortage of qualified medical personnel interested in inherited bleeding disorders.

In light of this situation, the CHS and the Association of Hemophilia Clinic Directors of Canada (AHCDC) have been seeking ways to encourage young physicians to develop interests in treating and doing research on inherited bleeding disorders. These far-sighted programmes offer our best hope of recruiting the new medical personnel that we need.

For the researchers that we already have, the important thing is to provide grant money to enable them to pursue their projects. Two major sources of research grant money are the Hemophilia Research Million Dollar Club and Canadian public at large. The Million Dollar Club is a repository for funds contributed primarily by members of the bleeding-disorders community, either individually or through CHS chapters. The initial idea was to raise $1 million and then use the interest derived from investing the money to support research aimed at finding a cure for bleeding disorders. Today the Club’s capital is approximately $1.2 million. During the past 10 years, the Club has provided over $1.5 million in research-grant money. The CHS also uses part of the money that we raise from the Canadian public to support research. For the past several years, the CHS has matched the amount contributed by the Million Dollar Club. This year, the Million Dollar Club and the CHS (with the support of Bayer Inc.) each contributed $100,000 for research grants.

Although the terms of reference of the CHS and the Million Dollar Club are broad enough to encompass both research directed towards finding a cure and research aimed at improving care with currently available treatments, the vast majority of the projects supported by the Million Dollar Club and the CHS have been aimed at finding a cure. Cure-related research is critically important. Unless cutting-edge researchers look for a cure, a cure will never be found. However, cure-related research rarely leads to short-term improvements in treatment. Three years ago, the CHS’s Programme Committee decided to look for a source of funds to support research aimed at improving treatment with currently available products; and the Genetics Institute (a division of Wyeth Pharmaceuticals) pledged $150,000 a year for three years to fund what we call the “Care Until Cure” research programme. This generous contribution has very significantly broadened the scope of research which the CHS is able to support.

Finally, it’s very important for an organization like the CHS to have a means of ensuring that the research-grant money that we allocate goes to the best qualified, most productive researchers. The way we do that is through the Hemophilia Research Grants Review Committee, chaired by Dr. Gershon Growe. Researchers, who want to obtain a research grant, submit proposals to the Committee, and expert members of the Committee decide which proposals are worthy of support and how to allocate the available funds. This method of determining who gets the grants is an example of a process called “peer review,” and this approach is widely regarded as the “gold standard” for the fair allocation of research-grant money.

The CHS is currently attempting to diversify the means by which we raise money to provide our services and to support research. If we are successful, the amount of money available to support research should increase substantially over the next decade.
NEWS UPDATE

UPDATE ON PRODUCT SHORTAGE
By James Kreppner, Chair, CHS Blood Safety Committee

An ongoing issue of concern to the Factor VIII community has been the continuing Kogenate FS shortage, and Bayer has recently updated the community on the progress it has been making with respect to this situation.

Bayer has reported that it is 80% complete in meeting its commitments made in response to the American Food and Drug Administration (FDA) observations on its manufacturing process, and that it is on track with a planned completion of the remaining 20% of planned changes. It expects that all but a few of the improvements will be completed by December. It will then be able to make more accurate predictions of product releases in early 2002, and hopefully resume a more normal release schedule by mid-2002 as the changed processes have their impact. It should also be noted that Bayer has been increasingly shipping larger amounts of product, with the most significant increase occurring in September.

This is all good news for those Canadian hemophiliacs who have been inconvenienced by being restricted as to the amount of product they take home per visit, or who have been in the difficult situation of delaying elective surgery while waiting for this problem to resolve. Hopefully, we will see a return to recombinant product based immune tolerance therapies for those individuals with inhibitors. Our community of patients and physicians should be recognized for their efforts to reduce demand during this crucial period. It has been difficult to maintain this lower demand, however, and demand has been climbing recently (although it is still below historical levels). This is understandable, as at a certain point, for example, elective surgery stops being elective. There is also a concern that the quality of care not be compromised.

No one should assume from the positive news that the problem is over; it is not. Until Bayer can return to the volume of its previous releases, we will continue to be concerned. However, we are now looking at mid 2002 rather than third quarter 2002 for potential normal deliveries, and that is an improvement. As well, Bayer has always recognized that the Canadian market is unusually dependent on Kogenate FS, and it has always made deliveries accordingly. As the Kogenate FS release situation improves, there is even greater confidence that Bayer will continue to meet its commitments.

It should be noted that the Kogenate FS product that can be expected in the next months will likely be the Special Access Program (SAP) product (the SAP product comes from newer 200 litre fermenters instead of the smaller 100 litre fermenters used for the licensed product). This 200 litre fermenter product is currently unlicensed in both Canada (although a license application is under review at Health Canada) and in the U.S. It is, however, licensed in Europe, and Health Canada has been permitting Canadian consumers access to this product through our SAP process. Bayer will substitute licensed product if it can, but again, for the present, the expectation is that the product used in the next months will be the unlicensed SAP product.

The Canadian Blood Services (CBS) deserves to be commended for its handling of this shortage. They have monitored the situation closely from the beginning and have regularly consulted the community. They have also taken precautionary steps such as the purchase, where available, of additional recombinant and plasma derived product. The CBS currently has a reserve of more than 20 million units of plasma derived product (the demand for plasma derived products had increased recently to 300,000 units per month from a historical average of about 60,000 units per month, but this increase has not continued into October). As the situation continues to improve, and the expiry dates approach on certain of the plasma derived lots, the CBS is cautiously exploring the alternative of reselling a portion of this plasma derived product back into the international market.

In sum, while the picture looks more positive than it did some months ago, we should remain vigilant, and attempt to follow the usage guidelines which can be found on the CHS website (www.hemophilia.ca). The cause and history of this shortage and a link to Bayer’s explanation can also be found on the CHS website. Anyone with particular questions or concerns should feel free to post them to the discussion area of the CHS website, or to email them to me directly at jkreppner@hotmail.com. Please also feel free to contact me either by telephone or regular mail via the CHS. Chair, CHS Blood Safety Committee.

CHS WELCOMES NEW STAFF

We are pleased to announce that CHS has recently hired two new Regional Program Coordinators. Marion Stolte will be responsible for co-ordinating programs and services for the bleeding disorders community in the province of Saskatchewan. The office in Saskatoon is now officially open. Marion may be contacted at:

Marion Stolte
CHS Regional Coordinator
Hemophilia Saskatchewan
2366 Avenue C North, Unit 213
Saskatoon, SK, S7L 5X5
Tel: (306) 653-4366
Fax: (306) 933-9664
E-Mail: mstolte@hemophilia.ca

Tradina Meadows will be responsible for co-ordinating programs and services for the bleeding disorders community in the 3 Maritime provinces, New Brunswick, PEI and Nova Scotia. Tradina may be contacted at:

Tradina Meadows
CHS Regional Coordinator
for the Maritimes
633 Main Street, Suite 650
Moncton, NB E1C 9X9
Tel.: (506) 389-7830
Fax: (506) 389-7829
E-Mail: tmeadows@hemophilia.ca
"Unfortunately, I think that there are a number of widows, parents, children and other relatives of hemophiliacs who died in the late 1980s or 1990s who simply do not realise they may be entitled to compensation from the 86 to 90 Hepatitis C Fund."

**B.C. GOVERNMENT EXTENDS COMPENSATION**

On September 24th, the British Columbia Government announced the decision to offer compensation to hepatitis C victims who were infected through blood products received either before 1986 or after 1990. B.C. joins Ontario, Quebec and Manitoba in announcing financial assistance to all victims in their province who were left out of the 1986-1990 compensation agreement.

**CANADIAN SCHOLARSHIP WINNERS**

The WYETH/Genetics Institute Hemophilia Group has recently announced that three Canadians are among the recipients of the Soozie Courter Sharing a Brighter Tomorrow Hemophilia Scholarship Program. The program was established five years ago to recognize the personal and academic achievements of young people with hemophilia throughout North America. Of the 17 students honoured for the 2001-2002 academic year, three Canadians from Western Canada have been granted scholarships. Cleaven R. Pagani, University of Victoria, Victoria, British Columbia is the winner of a $5,000 (US) college scholarship, while winners of the $1,000 (US) vocational scholarships include Chad O’Neill, British Columbia Institute of Technology and Lyf E. Stolte, Rosebud School of the Arts, Rosebud, Alberta. All winners have either hemophilia A or B. More than 60 entries were received for the 2001-2002 school year. Congratulations to Cleaven, Chad and Lyf!

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**WHERE ARE THE MISSING ESTATES? CAN YOU HELP?**

Hemophilia Today spoke with class counsel Bonnie Tough recently for an update on the 86-90 settlement. Bonnie expressed concern that there are a number of estates of persons who died prior to the settlement who have not come forward to claim from the Fund.

The settlement was designed to ensure that hemophiliacs who died before hepatitis C testing was widely available could nevertheless access the Fund. Anyone who died infected with HIV is deemed to have been infected with Hepatitis C. As long as the person used blood product one or more times from January 1, 1986 to July 1, 1990 and died infected with HIV there will be an entitlement to $72,000. A greater amount is paid if the family can prove that hepatitis C was a contributing factor in the death.

“It would be helpful if everyone in the hemophiliac community could try and spread the word to those who may not currently be involved in hemophilia. I think some of these people have simply lost touch with the community and do not realise their entitlement.”

Bonnie also commented that although she knew that in the past, some estates had great difficulty in satisfying the requirements of the Settlement and that there was unhappiness with the Administrator, the situation has improved dramatically in recent months, and all eligible claimants should be encouraged to apply.

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**Hemophilia 2002**

**Come and discover Seville!**

The Spanish Federation of Hemophilia selected Seville as host city for the XXV International Congress of the World Federation of Hemophilia based on its location, passion, culture, history and uniqueness. All people feel welcome by the warmth and charm of the Spanish people but above all, Seville is an atmosphere. Being out among its happy, celebratory crowds on a warm night is a not-to-be-forgotten experience. Discover a city that is both traditional and modern, diverse and unique.

**Program**

The Spanish Federation of Hemophilia and the World Federation of Hemophilia are working together to make this the most successful congress ever. As in past congresses, the program is divided into Medical tracks including Musculoskeletal and Dental sessions, and Multidisciplinary tracks (nursing, psychosocial, and other topics). Experts will present the latest developments in carrier diagnosis, prenatal diagnosis, treatment of orthopedic complications, treatment of HIV and hepatitis C, development and treatment of inhibitors, and other vital aspects of hemophilia. Special attention will be paid to issues relating to children and family, such as preventive medicine, quality of life, molecular diagnosis, gene therapy, and the application of advances in less developed countries.

In addition, special sessions will be presented prior to the congress such as a physiotherapy course, a laboratory workshop and psychosocial sessions and a segment designed especially for nurses. Look on our web site for more complete information and speaker names: www.wfh.org.

Industry Symposia sessions will bring you information on the latest advancements in products and their application to treating hemophilia. The cultural/social program also promises to delight you! From a culturally charged Opening Ceremony and Reception to a spectacular Music Concert at the world’s second largest Catholic Cathedral and the Gala Dinner, we promise to awaken your senses in every way. Relax amongst friends and build new contacts.

**Benefits – why come?**

- Meet and consult experts from around the world
- Gain and share knowledge with PWH and make new contacts in the Hemophilia community
- Learn about the latest advances in gene therapy, vCJD and other hot topics
- Relax and enjoy the warmth of Spain!


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HEMOPHILIA TODAY • FALL 2001
Focus On Research

CHS RESEARCH PROGRAMS

Supporting research towards improving the quality of life for persons with hemophilia and finding a cure have been goals of the Canadian Hemophilia Society (CHS) since it was founded in 1953.

CHS currently has three programs that support research: CHS Research Program, funded by The Hemophilia Research Million Dollar Club and CHS, with the support of Bayer; Care Until Cure, funded by WYETH/Genetics Institute; and the Aventis Behring-CHS-AHCDC Fellowship Program. A new fellowship program funded by Novo Nordisk will begin in 2002. The following reports describe the projects funded in 2001.

CHS Research Program

Since 1989, through funds provided by the Hemophilia Research Million Dollar Club and the CHS, the Society has funded basic scientific research grants and studentships aimed at developing treatments for hemophilia and finding a cure. The following reports describe the projects funded in 2001.

FINAL REPORT

Evaluation of a model system for a site-specific correction of hemophilic mutations

Dr. David Lillicrap

Background:
The objective of this research project was to further investigate the potential of a new strategy for repairing hemophilic mutations within the cells of hemophiliacs. This approach to gene therapy offers the most elegant solution to a genetic disease which we know is caused by discrete alterations to the genetic code for the clotting proteins, factors VIII and IX.

Approximately five years ago, two or three manuscripts appeared in the scientific literature describing a new method to repair genetic alterations within cells. In one of these papers, the investigators described studies in which ~50% of the liver cells in rats had undergone a genetic change as a result of this method.

In light of these very promising preliminary results we proposed to investigate the potential of using this method, so called chimeraoplasty, to repair mutations in hemophilia.

Experimental Results

The studies that we have carried out during the course of this research project have ranged from a stringent trial of the chimeraoplasty method in human liver cells in culture, to the eventual investigation of how this “mutation repair” process might be working and how it could be made more efficient.

After several months of trying to get the method to change a single nucleotide sequence in human liver cells without success, we realized that this experimental strategy was far more challenging than we had originally been led to believe. Furthermore, on attendance at international meetings and in talking with colleagues around the world, it was apparent that many other laboratories were having similar problems in getting any success with the method.

Despite these problems, and because of the immense potential of the method, we persisted with these studies, but tried to use the protocol in a much more simple experimental system, trying to alter the genetic code of a small DNA molecule from bacteria. However, here again our rate of positive results was still very poor.

After much discussion and thought, we decided to communicate with the laboratory at the University of Delaware in which the pioneering work on this method had been carried out. Subsequent to this contact, a graduate student from our laboratory, Brian Brown, visited the laboratory of Dr. Eric Kmiec for a two week period to see if we were overlooking any essential components of the method.

On Brian’s return to Kingston, despite incorporating new aspects of Dr. Kmiec’s methodology, we continued to experience very poor levels of genetic alteration. In light of these persistent problems, we have completed this project with a detailed analysis of molecular mechanisms that may contribute to the gene repair process. The rationale that underlies these studies is that if we better understand this repair process we may be able to improve its efficiency to a level where it may be applicable in the clinical setting. These latter mechanistic studies form the basis for the manuscript that will be submitted shortly to “Antisense and Nucleic Acid Drug Development”.

The Future of Chimeraoplasty

The funding provided for this project has enabled us to make a detailed evaluation of the potential use of the chimeraoplasty process for repairing hemophilic mutations. After significant efforts to enhance the efficiency of this process, we are left with the conclusion that this gene repair strategy is still some way away from clinical application. In theory it still offers the most elegant method to rescue hemophilia, but in practice, it is still an extremely inefficient process. Chimeraoplasty still generates controversy in the scientific literature and there are still a few very strong advocates for the methodology. Time will tell if the process can reach wider application.

In the meantime, we have now refocused our efforts on the area of conventional gene therapy using viral vector delivery of a normal canine FVIII gene to hemophilic mice and dogs.

In closing, we gratefully acknowledge the financial support of this project by the CHS Research Program and hope that we will be able to make further contributions to this area of hemophilia research in the future.
**INTERIM REPORTS**

**Secretion of Factors VIII and IX Following Myoblast Transplantation in Monkeys**

by Dr. Jacques Tremblay
Laval University

Hemophilia A and B are due to absence of factors VIII and IX respectively. The current treatment of these diseases with factors obtained from blood still presents some viral infection risks. The alternative treatment with recombinant protein is expensive. Moreover, injection with these factors is painful. Dr. Tremblay’s research group, therefore, proposes to develop a treatment based on the genetic modification and the transplantation of the patient’s own genetically modified myoblasts, i.e., the cells which form the muscle fibres.

Dr. Tremblay’s team is convinced that this goal can be reached since their research laboratory has already obtained very good myoblast transplantation results in immunosuppressed mice, i.e., a high percentage (90%) of muscle fibres expressed a gene (β-galactosidase) present in the transplanted cells (Kinoshita et al., 1994). This group has also obtained successful syngeneic myoblast transplantation in mdx mice without any immunosuppressive treatment (Viliquin et al., 1995d). Successful transplantation of monkey myoblasts labelled with β-gal gene introduced by a retroviral vector has also been obtained by Dr. Tremblay’s research group (Kinoshita et al., 1995b, 1996c; Skuk et al., 1999, 2000). Moreover, this research group has already demonstrated that when the gene for Factor IX is introduced into mouse myoblasts in culture these cells secreted Factor IX. Moreover, when these genetically modified myoblasts were injected into mouse muscles they secreted therapeutic levels of Factor IX in the blood of the animals.

Dr. Tremblay’s laboratory now plans to do experiments of Factor VIII and IX secretion in monkeys to obtain preliminary results which could lead to a clinical trial of this ex vivo gene therapy treatment. They aim to obtain a therapeutic level of either human Factor VIII or IX in monkeys by transplanting in their muscles myoblasts genetically modified in vitro either with the Factor VIII or the Factor IX gene using retroviral vectors. The secretion of Factor VIII or IX by these genetically modified myoblasts will be initially investigated in vitro. If the genetically modified myoblasts secrete enough factor in vitro, they will then be transplanted back into the same monkeys from which they originated (autotransplantation). The levels of secreted factor will be detected monthly (up to 12 months) in the host blood using a test with antibodies reacting specifically with the Factor VIII or IX produced by the transplanted myoblasts. These experiments in monkeys will therefore open a new era of treatment for Hemophilia based on Gene Therapy.

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**Novel Role of Gla Proteins in Blood Coagulation**

Dr. Mark Blostein
McGill University

Factor VIII and factor IX are two proteins that interact with one another to generate a blood clot in response to blood vessel injury. Their importance is highlighted by the inherited hemophilias, hemophilia A and B, that result from deficiencies of factor VIII and factor IX respectively. One goal of my research is to understand, at a molecular level, how factor IX and factor VIII interact with one another. In particular, my research will explore how a modification of factor IX, called gamma-carboxylation, is important for its interaction with factor VIII. Understanding these interactions at a molecular level will improve our understanding of the physiopathology of both hemophilia A and B. Approximately 10% of hemophilia A patients and 2-3% of hemophilia B patients develop antibodies (i.e. inhibitors) to exogenously administered factor VIII and factor IX respectively. These patients are not amenable to treatment with factor VIII or factor IX concentrates, and other methods are required to enhance blood coagulation. Recent work of mine has demonstrated that small helical peptides are able to enhance the function of factor IX. Therefore, another aim of my research will be to examine the biochemical properties of these peptides with the goal of developing novel therapeutic agents that can enhance blood coagulation in hemophilia patients with inhibitors.

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**Gene Therapy for Hemophilia A**

By Dr. Paul X. Liu

This project is to develop a novel method for gene therapy of hemophilia A. The novelties are to deliver the large human factor VIII (FVIII) gene in small pieces using the safe and efficient rAAV (recombinant adeno-associated virus) vector, and to enable these small pieces to come together and function properly.

Hemophilia A is the most common bleeding disorder and is caused by a deficiency or abnormality in blood coagulation factor VIII. Gene therapy is a promising future treatment, in which a functional FVIII gene is delivered to the patient to produce the coagulation factor. Among available molecular vehicles for gene delivery, the rAAV vector has several advantages (safe, efficient, long-lasting) over other vectors, but rAAV’s small packaging size prevents its use with the large FVIII gene. A miniature FVIII gene may be as small as 4.5 kb, but the final size will increase to well over 5 kb after the addition of accessory parts (promoter, regulator, etc.) that are required for efficient and regulated FVIII production. This final size is too large to be packaged into the rAAV vector for gene delivery. We will try to solve this problem by using a gene-splitting and splicing technique that we have developed recently.

continued on page 8
A functional FVIII gene will be split into two small pieces and modified by adding accessory parts including promoter, regulator, and splicing sequences. Each modified piece will be approximately 4 kb and within the size limit of the rAAV vector. These modified FVIII gene pieces will be delivered simultaneously into target cells using rAAV vectors, and the corresponding gene products are expected to come together and splice into a functional form of FVIII. Over the next two years, we will test this novel method initially in E. coli cells, then in cultured human cells, and finally in FVIII-deficient mice (an animal model of haemophilia). The production of FVIII and its therapeutic effect will be monitored.

Targeted Gene Therapy for Hemophilia
Dr. Andre C. Schuh

Although considerable progress has been made in the last few years towards a gene therapeutic approach to the treatment of Hemophilia, the optimal gene therapy strategy for this disease has not yet been defined. We propose to assess a novel gene therapy strategy for the treatment of Hemophilia A, using a mouse hemophilia model. Specifically, we propose to use genetic engineering and bone marrow transplantation to direct the expression of FVIII to bone marrow platelet precursors – cells that do not normally produce this coagulation factor. We anticipate that targeted FVIII will accumulate within circulating blood platelets, and that platelet activation at sites of blood vessel injury will result in local FVIII release, such that blood coagulation is specifically initiated at sites of bleeding. This approach would be expected to prevent secondary “re-bleeding” as well, and would also be predicted to be less likely to result in the formation of FVIII antibodies than are conventional treatment approaches. And importantly, we believe that this strategy would result in long-term disease control. At present, we are evaluating several complementary components of this strategy in our hemophilia mouse model. If successful, we anticipate that these mouse experiments will lead to analogous human studies.

Von Willebrand Disease and Exercise–Is it Worth the Sweat (Phase I):
Dr. Georges-Étienne Rivard

Von Willebrand disease affects approximately 1% of the general population. Affected women typically have excessive menstrual blood flow. The heavy bleeding that is characteristic of this disorder is due to a less than normal level of a protein called von Willebrand antigen. DDAVP is the drug that is currently used as first line therapy when medical intervention becomes necessary. This medication decreases menstrual bleeding by increasing the blood level of von Willebrand antigen. While this therapy has proven to be very effective, it is expensive and has considerable potential for unpleasant and sometimes serious side effects.

Several published studies have demonstrated that, in healthy persons, intense physical exercise can cause a similar increase in the blood level of von Willebrand antigen as compared to DDAVP. However, the impact of vigorous exercise on the severity of menstrual bleeding in women with von Willebrand disease has, to the best of our knowledge, never been studied.
The recently awarded grant from the Canadian Hemophilia Society and the Genetics Institute for the “Care until Cure” project is being used to fund part I of our study, in which we are investigating the effect of vigorous exercise on the level of von Willebrand antigen in forty healthy female volunteers. The study is being conducted at the Ste-Justine Hospital in Montreal. Dr. George-Etienne Rivard is the Principal Investigator of this study and Dr. Rochelle Winikoff is the Co-Investigator. Our follow-up study is designed to assess the effect of a home exercise program on the amount of menstrual blood loss in females with von Willebrand disease.

Given the high incidence of this disorder and the negative impact it may have on the lives of those affected, the prospect of a safe, effective and no cost alternative therapy to DDAVP is enticing. Our hope is that exercise, if proven to reduce menstrual blood loss, will become a viable treatment option for the treatment of von Willebrand disease.

**Interferon Alpha2b + Ribavirin Therapy for Individuals with Congenital Coagulation Disorder Infected with Hepatitis C with or without HIV Coinfection**

Dr. Jenny Heathcote

The above named study has multiple centres across Canada. This is necessary not only to recruit the sample size required (120) to be able to adequately assess the effectiveness of Interferon Alpha2b + Ribavirin in individuals with congenital coagulation disorders with chronic hepatitis C with or without HIV co-infection, but also it is hoped that this way the majority of infected individuals Canada wide can be included and thus receive free therapy for their chronic hepatitis C. The cost of the drug and of the nursing time required to administer the treatment has been covered by a successful grant application to CIHR and the industry, however, funding for the coordinator who needs to liaise with all the centres, collect the data and finally do the data analysis has been funded by “Care Until Cure,” as no funding was given by CIHR/Industry. It is essential in multi-centre trials to have a coordinator who can troubleshoot, manage the finances and liaise with all the interested parties as well as perform the analysis which is necessary to assess the efficacy of the two treatments that are to be compared, i.e., high dose induction Interferon therapy and Ribavirin versus standard Interferon therapy and Ribavirin.

Across the board, 41% of individuals infected with HCV respond to Interferon Alpha2b + Ribavirin. The response rate in those co-infected with HIV is unknown, as the viral load for hepatitis C tends to be higher in individuals with congenital coagulation disorders, particularly in those co-infected with HIV. It was felt that high dose induction therapy for the first eight weeks of treatment might enhance the effectiveness of antiviral therapy by 15%. This study has been designed so as to include a sufficient number of individuals in order to adequately assess whether induction therapy is or is not better than standard therapy.

**A prospective, randomized trial to compare two regimens of prophylaxis in older boys with severe Hemophilia A**

Dr. Manuel Carcao

Hemophilia A is a serious inherited condition associated with significant disability and health care resource utilization that results from a deficiency of coagulation factor VIII. Boys with the severe form of hemophilia A have frequent soft tissue and joint bleeds which, in many cases, result in severe and disabling joint disease by early adulthood. Traditional treatment is to replace the deficient factor after each bleeding episode. This limits the amount of bleeding and resulting damage but does not prevent further bleeding. Ideally, all patients should be placed on some form prophylaxis (administration of factor to prevent bleeds). Although optimal, primary prophylaxis (the infusion of factor on a regular basis instituted at a very early age to prevent any joint damage) is technically challenging because of the need for frequent venepunctures from a very young age, and furthermore is extremely expensive. Primary prophylaxis may also represent over-treatment for the small subset (~10%) of severe hemophiliacs who do not bleed frequently. Secondary prophylaxis (the administration of factor on a regular basis to prevent further bleeding once a child has developed joint damage) is an alternative strategy currently used in many hemophilia clinics.

Recognizing the high costs but inherent clinical value of prophylaxis, we have begun a research program to examine the cost benefit of a patient-driven (tailored) approach of prophylaxis, which may be less costly, and better accepted by families/patients, than standard prophylaxis, and which may be effective at preventing disability in hemophilic children. We feel it is essential to study a tailored approach to prophylaxis as the potential cost-savings could lead to a widespread adoption of this type of prophylaxis as a preferred therapy for hemophilia.

We propose to study two different approaches of prophylaxis in older children with severe hemophilia A. Children with severe hemophilia A between the ages of 2.5 and 15 years will be randomized to receive either standard prophylaxis or a lower dose/less frequent (tailored) prophylaxis regimen. The tailored regimen would initially involve administering only half the total factor VIII administered by the standard approach. The dose and frequency of factor VIII administered to patients on the tailored regimen will be modified (increased/decreased) according to preset steps if patients are having an unacceptable number of bleeds. Patients will be followed over 2 years to continued on page 10
determine the incidence of bleeding, joint damage, joint x-ray changes and direct and indirect costs.

By studying these two treatment regimens we may be able to determine if the tailored regimen can provide effective prevention of bleeds and joint damage at lower cost and less patient inconvenience. If it is determined that a less intense regimen of prophylaxis is cost-effective, then substantial savings will result when instituted throughout the Canadian hemophilic population. Additionally, if it is shown that a less frequent and more convenient regimen of prophylaxis is effective, then more patients may be willing to be placed on prophylaxis. Since, ideally boys with hemophilia should be on prophylaxis, this study may determine a prophylaxis regimen, which will be affordable, effective and acceptable to parents and patients. As a result, this new tailored regimen is likely to be attractive to funding agencies, become more widely adopted, and improve the health care and quality of life of hemophilic patients.

NEW FELLOWSHIP PROGRAM

Hemostasis Management Fellowship Program: Hematology in Action

Novo Nordisk Canada Inc.–
CHS–AHCDC Fellowship in Congenital and Acquired Bleeding Disorders

The Novo Nordisk Canada Inc., Canadian Hemophilia Society and Association of Hemophilia Clinic Directors of Canada Fellowship in Congenital and Acquired Bleeding Disorders is a new fellowship program established in the fall of 2001. Novo Nordisk has a leading position within areas such as coagulation disorders, and manufactures and markets pharmaceutical products and services that make a significant difference to patients, the medical profession and society.

The goal of this new fellowship program is to provide fellows in hematology or other related fields the opportunity to gain clinical or research skill, to improve the care and quality of life of patients with hemophilia and other congenital or acquired bleeding disorders.

For more information regarding this new program, please contact Joyce Argall Gouin at 1-800-668-2686.

**Aventis Behring – CHS – AHCDC Fellowship in Hemophilia**

*The Aventis Behring, Canadian Hemophilia Society and the Association of Hemophilia Clinic Directors of Canada Fellowship in Hemophilia Program was established in the year 2000. Aventis Behring is a global leader in the plasma protein industry, providing a wide range of innovative, high quality therapies and unique support services worldwide.*

This fellowship program provides fellows in hematology or other relevant fields the opportunity to obtain clinical or research skills necessary to improve the care and lives of patients with inherited bleeding disorders. The following report describes the project funded in 2001.

**Fellowship Report**

Dr. Rochelle Winikoff

This award will allow me to pursue a second of a two year training program in hemostasis at Ste-Justine Hospital in Montreal under the guidance and supervision of Dr. Georges-Étienne Rivard, who is a full clinical professor at the University of Montreal in Quebec as well as a recognised national leader in hemophilia.

As a certified hematologist, this extended training will enable me to acquire a high level of expertise in the coagulation laboratory, in the treatment and management of adults and children with bleeding disorders, especially in hemophilia, and to pursue my ongoing clinical research projects in hemostasis. In fact, a first study relating to von Willebrand disease, of which I am the co-investigator, is already complete and will be submitted in abstract form for the upcoming 2002 World Federation of Hemophilia meeting in Seville, Spain. Recruitment for a second related study in von Willebrand disease has just begun. As well, in the upcoming year, I will embark on a third study related to hemophilia. My current enrolment in a Master’s thesis program in Epidemiology and Biostatistics at McGill University undoubtedly endow me with the necessary skills that will enable me to proceed autonomously in my future research endeavours in hemostasis.

My future goal is to become director of a hemostasis clinic devoted to the comprehensive care and follow-up of patients with bleeding disorders in a designated academic centre and to remain active in clinical research. In short, the financial support for the upcoming year will enable me to take significant strides in the advancement of my personal training, which in turn will prepare me for a lifetime career in hemostasis.
Gene-therapy for Hemophilia—Ideas and Concepts

By Cyrus Salimi
Hemophilia Ontario, Toronto and Central Ontario Region

Introduction:
Finding a cure for hemophilia has long been a dream of people with hemophilia and their treaters. Gene-therapy is one promising method that may achieve this goal. There have been promising results in animal models, where genetic engineering of gene therapy vectors continues to produce substantial increases in clotting factor levels. Clinical studies are expected to confirm these results, showing that these models will serve as a reliable guide to treatment in humans. Now that these clinical trials of gene therapy for hemophilia are underway, after years of preclinical studies, the early results are encouraging, demonstrating safety and evidence of gene transfer and expression.

Why is hemophilia a good disease for gene therapy?
Hemophilia attracts a lot of gene-therapy research, because so much is known about transmission of the disease, the location and the structure of the gene, and the structure and function of the factor produced from the gene. Importantly, the level of Factor VIII or IX in the blood achieved is not critical once it is above a threshold of around 5% - the baseline FVIII or F IX is less than 1% in severe hemophilia and between 2-5% in moderate hemophilia. If researchers can increase the amount of Factor production to maintain the level somewhere above 5% and keep it at that level, then they will have converted severe or moderate hemophilia to the mild form. People with mild hemophilia generally do not suffer from spontaneous bleeding. Increasing the level of Factor VIII or IX further, up to 25%-50%, would mean people with hemophilia would have a similar bleeding tendency to the general population.

How does gene therapy work?
In gene therapy experiments, researchers transfer F VIII or F IX producing genes into the cells of the hemophilia patient, causing these cells to produce the factor that is missing. Three essential elements are necessary for this gene transfer: the gene delivery vehicle or vector, the gene to be transferred and the specific target cell. Most researchers use viruses as vectors or carriers of the gene of interest. The viruses which have been used most include retroviruses, adenoviruses, and adeno-associated viruses. Researchers make changes in the virus to prevent reproduction of the virus inside the cells. Because of adverse effects of some viral vectors, researchers are also attempting to use non-viral vectors for gene therapy.

What obstacles remain to gene therapy in humans?
Several practical obstacles remain, which need to be investigated and eliminated. Our body has a natural defence system, which rejects foreign material introduced to it. Therefore the body may reject the gene or destroy its product. Another troublesome issue is packaging the Factor VIII producing gene and delivering it into the cell. This gene is very big, which makes it difficult to transfer it into the cell. One way of doing gene transfer is to take some cells from the person’s body and transfer the gene into them using a virus which is altered to make it harmless. Cells, which have been considered for this type of gene transfer, include bone marrow cells, connective tissue cells such as fibroblasts and muscle cells, the endothelial cells that line the inner layer of the lumen of blood vessels, cells lining the interior of the intestine and liver cells. Any cells targeted must survive a long time and have easy access to the blood circulation.

Different studies have been done on different cells to examine the accessibility of the cells to a wide range of manipulations in gene-therapy. An example of one of these studies will demonstrate the problems. Gut epithelium is an attractive target for gene-therapy of hemophilia due to the large number of rapidly dividing cells. Lozier et al. at the Clinical Gene-Therapy Branch of the National Human Genome Research Institute of Bethesda used an adenovirus vector and found that small and large intestine epithelial cell lines are capable of synthesizing factor VIII and factor IX in the lab. When they did the same study in the Rhnes Macaque monkey, the results were disappointing. Intravenous injection of a factor IX producing virus had no effect at its lowest dose, but at the highest, it produced significant levels of human factor IX for approximately 3 weeks. Unfortunately this benefit was secured at the cost of severe and likely permanent liver damage manifested by high liver enzyme levels and persistent low level of fibrinogen, another blood factor necessary for clotting. The experience of Lozier et al. shows that there may be a very narrow window between the effective dose and the toxic dose. Even if this liver toxicity can be avoided, another problem may become apparent. Lozier also found that the recombinant human factor IX produced was highly immunogenic, which means the macaque monkey’s immune system reacted against that to destroy it.

Another problem is that adenovirus is the common cold virus and most people have therefore been exposed to it and are immune to it, so it is highly possible that we may expect the immune response induced by the vectors to be accelerated and more intense than effects generated in naïve animals. Adeno-associated viruses are another group of viruses which were used for gene therapy. Recently a modified factor VIII gene has been incorporated into an aden-associated virus vector and sustained hemostatic levels of factor VIII have been produced in mice. Time will tell what problems these vectors may have.

What is happening in current human gene therapy trials?
Three trials of gene therapy in persons with hemophilia A and B are now under way. One study in patients with hemophilia B is evaluating the safety of intramuscular injection of an adenovirus vector. The second study involves patients with severe hemophilia A, treated by intravenous injection of a murine...
Mild Hemophilia A
in Newfoundland

By Mary Frances Scully, M.D., FRCP
Hemophilia Clinic Director, Newfoundland & Labrador

During a recent traveling clinic to Western Newfoundland, I had the very unusual diagnosis of mild hemophilia for the first time in a 68-year-old gentleman. This man was referred to me by our genetics counselor, David Macgregor, who had noted that a number of the man’s brothers have mild hemophilia A. He, in turn, told me that he was in fact diagnosed as a bleeder by the legendary Dr. John Olds, a surgeon born into a wealthy American family, who was educated at Johns Hopkins University and then chose to dedicate his life to developing health care services for people living in the fishing outports of central Newfoundland. I am fascinated with this particular patient’s history as I had read Dr. Olds’ biography to see whether any reference would be made to a high prevalence of a bleeding disorder in the region and could find none. However, our patient told me that as a young boy he presented with a painful swollen ankle to Dr. Olds who strapped the ankle very tightly and warned the boy and his family that he was a bleeder. As a young man he worked in the woods; on three occasions, he had accidents involving an axe and each time he was hospitalized and required up to five units of blood to stop bleeding. On three occasions he has had teeth pulled and on two he has had bleeding lasting a week requiring resuturing of the sockets. He now has extremely severe “osteoarthritis” which is asymmetria.

leukemia retrovirus vector containing the factor VIII gene. In the third study skin fibroblasts from patients with severe hemophilia A were grown in culture, the factor VIII gene was inserted into them and then implanted into the fat inside the belly. Six patients with severe hemophilia A have been treated with this method, all of whom had chronic hepatitis C and four of whom had HIV infection. Four patients had measurable plasma levels of factor VIII and their frequency of bleeding was decreased. Two individuals had no spontaneous bleeding episodes for nearly 10 months, for the first time in their lives, although these favourable effects were transient and did not last more than 10 months. No serious adverse effects were reported.

What potential problems with gene therapy are expected?

Although the preliminary data are encouraging, several questions remain. The plasma levels of factor VIII or IX achieved so far by gene therapy are insufficient to free patients from the need for coagulation factor injections. Levels of at least 5% are required to prevent episodes of spontaneous bleeding and to guarantee that supplementary factors are needed only in cases of trauma or surgery. The risk of developing inhibitors remains a concern, particularly in previously untreated patients. HIV-infected patients who are receiving highly active antiretroviral therapy may have a poor response to retrovirus-based approaches, and those with hepatitis may have a poor response to the insertion of viral vectors into the liver.

A potential consequence of gene therapy is the introduction of foreign DNA into the germ cells of these individuals, resulting in the transmission of the donated gene sequences to subsequent generations. If this resulted in permanent correction of the genetic defect, it could hardly be viewed as a deleterious side effect. However, most vectors integrate randomly. The donated sequences may result in harm to offspring if the site of the integration disrupts a critical gene sequence in the developing embryo or if expression of the donated gene sequence somehow disrupts the normal program of development. Thus one of the safety assessments of every gene-therapy strategy is a determination of the likelihood that donated gene sequences will be transmitted to future generations. So far there has not been any evidence of this germline transmission of vector sequences in the ongoing hemophilia trials.

Why are there so many different types of strategies to gene therapy?

On the basis of considerations discussed above, it is likely that in the case of hemophilia, more than one successful gene-based approach to treatment will be developed. In a sense this can be viewed as analogous to the situation with antibiotics. Multiple antibiotic drugs are available, and physicians choose the most suitable one on the basis of the organism to be treated and the side effects of the drug. In the case of hemophilia, the disease is the same, but patients differ considerably with regard to their particular condition, which may influence the choice of treatment. Some patients are on retroviral drugs and cannot be treated with retroviral vectors, while others with liver disease from hepatitis infection may not be good candidates for liver directed treatment approaches. At this time the hemophilia population is probably best served by the continuous simultaneous development of multiple approaches. One of the major challenges of the next few years of clinical research in this area will be to define which subgroups of patients can be most safely and effectively treated with which approaches. Approaches that are safer and more effective will become the benchmark standards against which new strategies will be assessed.

Summary:

In spite of all these difficulties, hemophilia is likely to be the first common severe genetic disorder to be cured by gene therapy. Affordable gene therapy will be particularly important for people with hemophilia in developing countries who have little access to expensive recombinant factors. Despite encouraging early results, it should be kept in mind that at this time there are no licensed gene therapy products, and that even for well-established classes of pharmaceuticals the time from initial clinical trials to licensing of a product may be anywhere from 2 to 10 years. Researchers hope that by the year 2004 we will have had full success in gene therapy for hemophilia.
Although mild hemophilia has been reported in the literature since 1953, the largest cohort study published to date includes only 55 patients and is confined to patients less than 17 years of age. Anecdotal evidence from small case series suggests that patients with mild hemophilia, although they do not tend to bleed spontaneously, can have the same spectrum of significant bleeding disorders as patients with moderate and severe hemophilia if they experience trauma or surgery. However, perhaps because the nature of the bleeding tends to be more episodic, both patients and their care providers often do not appear to persist in investigations and hence, there is frequently a very long delay in time to diagnosis and, at times, to treatment. Traditionally, those affected by mild hemophilia have relatively little involvement with comprehensive care hemophilia clinics and the hemophilia societies. Therefore, members of such families are often not aware of the potential health risks associated with their condition and may not have access to the most up to date information.

The high prevalence of some type of bleeding disorder in central Newfoundland was noted by family physicians working in the area in the sixties. Dr. Fred Woodruff, a retired physician, has been kind enough to share with me a copy of a study written by Ronald Delaney, a student working in the area, which was published in 1972. In the seventies, Dr. Eileen St. Croix, a local family physician, worked with Dr. Elizabeth Ives from the genetics department of Memorial University of Newfoundland to identify a large kindred of patients with a sex-linked inheritance pattern consistent with hemophilia. Coagulation studies confirmed a diagnosis of mild hemophilia A. Thanks to the hard work of Dr. St. Croix, expertise in the management of mild hemophilia has been developed locally. Patients were treated initially with cryoprecipitate and then factor concentrates. However, Dr. St. Croix was also concerned as she had noted an increase in liver enzymes post treatment in a number of patients and introduced DDAVP as first-line therapy. Many patients in the region have since been successfully treated with DDAVP for minor bleeds. Despite this, however, a number of patients from the region have become infected with HIV and Hepatitis C. This tragedy has led to a great distrust within the community of hemophilia treatment and treaters.

Due to a shortage of hematologists in Newfoundland in the eighties and early nineties, it was not possible to develop traveling clinics in the region. The majority of patients from this area were unable or unwilling to travel to the comprehensive care clinic in St. John's. In 1997, a review of hemophilia program charts revealed that 70% of patients with hemophilia in the province had been lost to follow up. Therefore, new efforts were made to develop a comprehensive care team based at the Health Sciences Corporation and to begin traveling clinics. After consultation with local physicians and caregivers, it was elected to develop traveling clinics in central and western Newfoundland. The first clinics were held in 1999 and clinics to both areas have been held approximately every six months with great success. In particular, as physiotherapist services are very limited in rural Newfoundland and there is very limited access to specialized laboratory testing, the presence of the team physiotherapist, currently Andrea Hann, with the chief technologist from the hemostasis laboratory, Michelle Hendry, along with the nurse coordinators, initially Charlotte Sheppard and now Marilyn Harvey, and myself, Dr. Scully as medical director, has been much appreciated by patients and the local health care providers.

I had first become interested in the high prevalence of hemophilia in Newfoundland after working with Professor Alan Giles and Dr. David Lillicrap at Queen’s University in Kingston. In 1998, Dr. Yagang Xie, who also received part of his training with Dr. Lillicrap at Queen’s, joined the faculty at Memorial University and became Director of the Diagnostic Molecular Laboratories. Soon after his arrival, Dr. Xie successfully applied to the Aventis Behring Research Funds to begin working to identify the mutation leading to the high prevalence of hemophilia in this community. Dr. Xie’s laboratory, in collaboration with Dr. David Lillicrap at Queen’s and Dr. R. Bagnell at King’s and St. Thomas’ School of Medicine in London, have successfully identified the point mutation, valine 2016 to alanine which causes the high prevalence of mild hemophilia.

In our pilot studies, David Macgregor, our genetic counselor, has identified a large kindred of over 1800 members spanning ten generations in the pedigree. Of 112 identified patients, 83 are living, 82 are male and 1 is a homozygous female. 109 obligate carriers have been identified and there are 232 women, who due to their place in the family pedigree, are at risk of carrying the mutation. Our research team has now expanded to include Dr. Brendan Barrett, a clinical epidemiologist, Dr. Bruce Sussex a cardiologist, and Dr. Eilish Walsh, a pediatric radiologist. We also hope to work with Dr. Mark Pickett, Director of Research and Scientific Relations at Bayer, who has expressed his interest in supporting this project.

We now propose detailed studies to look at the impact of this bleeding disorder in the community. In particular, we will focus on the prevalence of musculoskeletal and cardiovascular problems in affected members of the community. In women, we will also look at the prevalence of menorrhagia (heavy periods), post partum hemorrhage (bleeding post delivery of a baby), and hysterectomy. We will also look to see at what age the disorder was diagnosed, how the diagnosis was made, whether by family studies or because it was picked up due to abnormal bleeding, the pattern of bleeding among patients, and their use of blood products.

We have now had four clinics in the region. Our preliminary impression is that there are patients diagnosed with mild hemophilia A who have had very significant problems. We hope that our studies will confirm our preliminary impression that mild hemophilia A can have a very significant clinical impact. If this is true, this will have important implications such as the need for much more rigorous screening in the pediatric population and inclusion of awareness of hereditary bleeding disorders in other public health and wellness initiatives.
Introduction
The Canadian Hemophilia Society and the hemophilia clinics rely on computerized information to help advance hemophilia care. The information can be used to lobby government, to plan research, to document care, and to help manage the supply of factor concentrates.

Recently, the CHS used statistics from the Canadian Hemophilia Registry (CHR) in negotiating the federal compensation package for hepatitis C compensation; researchers at the Hospital for Sick Children used information from CHR to find out if there were enough young children to conduct the Canadian Prophylaxis study, and clinics used the clinic database (CHARMS) to identify the whereabouts of specific lot numbers for recall. It is now difficult to imagine how we could continue to be successful without such ready access to information. New uses for CHARMS are being continually developed; for example, the nurses group (CANHC) is developing a database to ensure that phone advice is being standardized across the country.

The two computerized databases, CHR and CHARMS, are under the complete control of the clinics, and no other organizations can access them. Whenever information is given out, it is coded and doesn’t have any names attached. This means that the information is as secure as everyone’s hospital or clinic record.

The Canadian Hemophilia Registry (CHR)
This database was started in 1988 by the clinic director’s group (the Association of Hemophilia Directors of Canada – AHCDC). The first purpose was simply to find out how many people with hemophilia there were in Canada. Later the database was used to count the number of people with HIV and hepatitis C.

CHR is a single and central database to which each clinic supplies information on every person. The information is restricted to the type of factor deficiency, the severity, the date of birth, and the HIV and hepatitis C status. No names are included; each individual is identified by a code known only to his or her clinic. Even the director of the CHR cannot identify the individual whose data he is looking at. CHR then assigns a number for each individual (the “CHR number”) and gives it back to the person’s clinic. The clinic can then use that number when it needs to send out confidential information on individuals. For example, the clinics may need to send out blood samples to a central laboratory for a research project. In that situation only the CHR number would be on the tube; that is, there are no names.

Each year, or whenever information is needed, the CHR provides summary data on the Canadian Hemophilia population. No individual data is supplied, and only national summaries are given out. Provincial summaries are not publicly given out, but may be supplied to any clinic which asks for it. The information from CHR has also resulted in a number of published articles.

A lot of work goes into keeping the CHR up to date, as there are many changes, due to movements of people around the country, immigration both in and out of the country, newborns, and deaths. The maintenance of CHR is entirely voluntary; no pay is available; fortunately everyone realizes how valuable it is, so it runs on commitment.

The Canadian Hemophilia Assessment and Research Management System (CHARMS)
CHARMS therefore is like a computer program such as Word or WordPerfect; many people have these programs but each person has only his own files.

CHARMS can store any kind of information normally kept in a chart, but more as well. A very important function of CHARMS these days is to keep track of blood products so as to maintain supplies and give early warning of shortages. For example, a clinic recently identified that one of its regional hospitals was storing forty vials of a product about to outdate; the regional CHR coordinator was notified and the supply was used elsewhere.

Information on blood product use in CHARMS is sometimes exported from clinics to CentrePoint, which is a single computer in the head office of the clinic directors group (AHCDC). CentrePoint collates information from the clinics so as to provide national data. The information which is sent from the clinics is entirely anonymous; only CHR numbers are attached to the information, no names or addresses or HIV data.

Privacy and Confidentiality
Both the CHS and AHCDC are determined to maintain people’s privacy. All information that is given out is coded, neither of the two databases are linked to other databases, all data is managed by health care professionals, and all databases are being moved to McMaster University Medical Centre, behind two “firewalls.” International standards, particularly those of the Canadian Standards Association (CSA) are followed. Canadians played major roles in a seminar on Privacy and Confidentiality at the World Federation of Hemophilia.

History
The CHR and CHARMS databases are proving to be invaluable, but they did not appear overnight. Many people have been involved in their development, both directly and indirectly, over a long period of time. As early as 1978 the need for a database was articulated at the Society’s first Winnipeg conference on comprehensive care. A year or two later Dr. Ron George, a computer scientist and Life Member, and his son Mark, also a computer scientist, programmed a computer for a database designed by Dr. Martin Inwood and used for a research project conducted by the London and Hamilton clinics. In 1993 the CHS hosted a national conference (now remem-
Profile

Dr. Irwin Walker

By Barry M. Isaac, Ph.D.

Dr. Irwin Walker, Medical Director of the Hemophilia Program, McMaster Division, took up the study of medicine because one of his parents, his father, was a family physician. According to Dr. Walker, his father simply “liked” the practice of medicine and took a great interest in his patients. On occasion, his father would make some remarks about his practice or his patients, which was enough to make Dr. Walker interested in his father’s work, for Dr. Walker was “not very keen on anything” but was “normally rebellious” as are most young people. He thought he might take up engineering, but he was too unfocussed to make a firm decision about what sort of engineer he wanted to be. So, with his father’s gentle prodding, he entered the Faculty of Medicine at The University of Melbourne.

Something else his father told him that made him curious about dealing with people was that “patients are afraid.” He took notice after hearing this, and he suggests that it was this insight that really piqued his interest, for he began to “ferret out those fears” in his patients as he attempted to care for them. A telling comment from Dr. Walker is that he greatly dislikes the term “consumer” when it is applied to patients. He strongly feels that viewing his patients as simple consumers devalues the relationship between the doctor and his patient.

Dr. Walker’s interest in hemophilia began during his first year of residency because one of his instructors took extra time and effort in the laboratory. Dr. Walker often found himself, along with a few other interested students, spending extra time in the laboratory working on coagulation problems simply because of the time and effort shown by this instructor.

But in 1971, when he moved to McMaster University, he ran into two other treaters of hemophiliacs, Dr. Alvin Zipurski and Dr. Mohan Pai, who asked him to help them with their work. They taught him a lot and subsequently provided an ongoing pediatric perspective which helped him when young patients grew to adulthood and came under his care.

Shortly after this, he encountered the formidable figure of Dr. Martin Inwood, who Dr. Walker credits with being the single biggest influence on his hemophilia medical career. Any who have come into contact with Dr. Inwood, whether physician or hemophiliac, will attest to his charisma and his mentoring skills.

Dr. Inwood was in the initial stages of trying to put together a data collection system that would aid in the treatment and care of hemophiliacs by gathering the utilization of blood products from several clinics (the desire was to link all the hemophilia clinics). While the initial programme was relatively modest, it grew until it eventually collapsed under its own weight. But the failure of this initial attempt ought not to be viewed as the failure of all such data collection. Dr. Inwood saw this, and so did Dr. Walker, who has picked up the reins and been instrumental in designing a new programme. And some of the data collected by the initial system proved to be curious, to say the least.

Dr. Walker put together some of the figures they had gathered and presented a paper at the World Federation of Hemophilia meeting in Rio di Janiero in 1975. This revealed that 25% of all coagulation products issued to hemophiliacs simply disappeared—there was no accounting for them. This was a worrisome development for Dr. Walker and his colleagues in the hemophilia treaters community. How could they ask the government to supply an increased volume of coagulation products if some 25% of the currently supplied products could not be traced or accounted for? These concerns led Dr. Walker to begin investigating other means to begin gathering data on coagulation utilization.

He first looked at the “McChip” programme developed at McMaster. While it offered promise, it was not quite what Dr. Walker and others deemed necessary for the task. And so he, along with a team of software developers at McMaster University, began to work on a new programme that would, at a minimum, track the management and utilization of blood products. Once that module had been developed, Dr. Walker convinced 28 hospitals to participate and use the programme, which became known as CHARMS (The Canadian Hemophilia Assessment and Research Management System). CHARMS provided a way, for the first time, to trace the movement of coagulation products as they moved from the Canadian Blood Service to various hospitals or Comprehensive Hemophilic Clinics and then out to patients, who have to keep accurate records of how they used the materials. The inventories of product had to balance. For the first time there is a system to determine how these precious materials are used. And for the first time the data gathered by the programme will be made available with the help of Aventis Behring, who have provided funds for publication.

While these advances are important for hemophilia care, Dr. Walker feels that the most important improvements have been four-fold: comprehensive care clinics, recombinant factor products, prophylactic therapy for young hemophiliacs and the joint advocacy efforts that have been made to governments by the CHS and the medical community. These efforts have been “enormous,” in Dr. Walker’s opinion, and have made a distinct difference in care for hemophiliacs. Linking the voices and efforts of the patients and caregivers has developed a “powerful way to do medicine,” Dr. Walker says. And this has had a profound effect on Dr. Walker’s career, for, as he says, this working relationship stands alone in its importance for his working career. One is tempted to say that Dr. Walker’s work with the hemophilia community over the years has had a singular effect on the lives of Canadian hemophiliacs as well.

COMPUTERS CONTINUED

HEMOPHILIA TODAY • FALL 2001

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Dr. Walker put together some of the figures they had gathered and presented a paper at the World Federation of Hemophilia meeting in Rio di Janiero in 1975. This revealed that 25% of all coagulation products issued to hemophiliacs simply disappeared—there was no accounting for them. This was a worrisome development for Dr. Walker and his colleagues in the hemophilia treaters community. How could they ask the government to supply an increased volume of coagulation products if some 25% of the currently supplied products could not be traced or accounted for? These concerns led Dr. Walker to begin investigating other means to begin gathering data on coagulation utilization.

He first looked at the “McChip” programme developed at McMaster. While it offered promise, it was not quite what Dr. Walker and others deemed necessary for the task. And so he, along with a team of software developers at McMaster University, began to work on a new programme that would, at a minimum, track the management and utilization of blood products. Once that module had been developed, Dr. Walker convinced 28 hospitals to participate and use the programme, which became known as CHARMS (The Canadian Hemophilia Assessment and Research Management System). CHARMS provided a way, for the first time, to trace the movement of coagulation products as they moved from the Canadian Blood Service to various hospitals or Comprehensive Hemophilic Clinics and then out to patients, who have to keep accurate records of how they used the materials. The inventories of product had to balance. For the first time there is a system to determine how these precious materials are used. And for the first time the data gathered by the programme will be made available with the help of Aventis Behring, who have provided funds for publication.

While these advances are important for hemophilia care, Dr. Walker feels that the most important improvements have been four-fold: comprehensive care clinics, recombinant factor products, prophylactic therapy for young hemophiliacs and the joint advocacy efforts that have been made to governments by the CHS and the medical community. These efforts have been “enormous,” in Dr. Walker’s opinion, and have made a distinct difference in care for hemophiliacs. Linking the voices and efforts of the patients and caregivers has developed a “powerful way to do medicine,” Dr. Walker says. And this has had a profound effect on Dr. Walker’s career, for, as he says, this working relationship stands alone in its importance for his working career. One is tempted to say that Dr. Walker’s work with the hemophilia community over the years has had a singular effect on the lives of Canadian hemophiliacs as well.
While we have been talking about the reality of women and bleeding disorders for a number of years now, it is only within the hemophilia community that the fact that women are affected by bleeding disorders is truly recognized. Studies continue to show that women suffering from menorrhagia are rarely tested for coagulation disorders despite the fact that menorrhagia is one of the most prevalent symptoms of this condition in women.

In a study done in Germany (1), 153 females who presented with menorrhagia underwent numerous coagulation tests. 61 of the 153 tested (40%) showed a coagulation disorder. Of these, 37 (24%) had vWD. The rest were divided into platelet disorders, the hemophilies and fibrinolytic disorders. The median age of diagnosis was 36, despite the fact that the median age at the onset of menstruation was 12. It has also been shown that 69.1% of women with vWD have a history of anemia compared to 1.3% of a control group. (2)

In a recent presentation to the American College of Gynecologists and Obstetricians, Dr. Andrea Luke stated that a significant proportion (12%) of women presenting with menorrhagia have an underlying bleeding disorder. She found that 6% of the women in her study had vWD, while the other 6% had various disorders. She urges doctors to do proper diagnostic testing for a coagulation disorder before treating a woman for menorrhagia. The results will affect the treatment options offered to her.

Juvenile Uterine Bleeding (JUB) should be considered as a first symptom of an inherited bleeding disorder. Of 250 patients with JUB in a study in Moscow (3), 163 were found to have various hemostatic problems. Forty girls (25%) were found to have vWD.

A study done at the Royal Free Hospital in London, UK (4) showed that menorrhagia is a common complaint in women who have been diagnosed with a coagulation disorder. A study which included 116 previously diagnosed women showed that 74% of those with vWD, 57% of those with hemophilia VIII or IX and 59% with Factor XI suffered from menorrhagia. This is much higher than the norm where 9%-14% of the population experience menorrhagia. (4)

The complexity of the laboratory tests for vWD and platelet disfunctions makes it even more difficult for women to be properly diagnosed. Routine screening tests, including prothrombin time (PT), partial thromboplastin time (APTT) and bleeding time may provide clues to the presence of a coagulation disorder. However, normal screening tests should not rule out the possibility of a congenital bleeding disorder: the physician must rely on careful personal and family histories to determine whether full laboratory evaluation is indicated. (5)

At the Canadian Association of Gynecologists and Obstetricians Annual Congress held in St. John’s, Nfd. in June of this year, Dr. Mary Frances Scully, hematologist with the St. John’s treatment centre and Dr. Gillian Oliver, pediatric gynecologist from Hamilton, presented on the diagnosis and treatment of menorrhagia caused by a bleeding disorder. This type of presentation will increase awareness amongst medical personnel leading to an increase in proper diagnosis and treatment.

Because the scope of this disease is only beginning to be recognized, many women are still undiagnosed. Studies into menopause and the effects of hormonal changes that accompany it are just beginning. Many women who would now be at this stage in life, especially those who have had severe menorrhagia in the past, have often had hysterectomies and therefore no longer bleed. Once women are properly diagnosed, more research into diagnostic tools and treatment options as well as its effects at different times in a woman’s life will be undertaken.

References:
1. Coagulation disorders in women with menorrhagia: Krause et al., Haemophilia, Volume 6 no. 4, June 2000
2. Obstetrical and gynecological characteristics of vWD in comparison to the general public: Kouides et al., Haemophilia Vol. 4 no.3, May 1998

NEW SLIDE PRESENTATION FOR THE GENERAL PUBLIC — You CAN stop the bleeding

As part of its efforts to raise awareness in the general public about bleeding disorders in women, the CHS has developed a slide presentation based on one created by the NHF to show basic information on von Willebrand Disease. It is called: You CAN stop the bleeding. The presentation kit includes slides, overhead transparencies and a PowerPoint presentation, speakers notes to accompany the slides, tips for presenters, an information handout, and various educational materials to offer to the audience. This kit is aimed at the general public who have no knowledge of bleeding disorders. Due to the fact that VWD affects women more than men because of

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HEMOPHILIA RESEARCH MILLION DOLLAR CLUB REACHES NEW LANDMARK

by Frank Bott, Chair, Hemophilia Research Million Dollar Club

The Hemophilia Research Grants Review Committee, under the chairmanship of Dr. Gerry Growe, earlier this year announced the 2001 grants recipients (as listed on page 6 of this edition of Hemophilia Today). These grants total $200,000 in value, and were made possible by funding provided by the Canadian Hemophilia Society and the Hemophilia Research Million Dollar Club. From 1991 to this year the Million Dollar Club has contributed $1,500,000 to the CHS, making the Club the principal supporter of hemophilia research in Canada. Last year we acknowledged in Hemophilia Today the Canadian Hemophilia Society and all its chapters and regions, and the individuals, families and groups who have made this possible by becoming members of the Million Dollar Club or have supported us through their donations. This year we recognized them in the ‘Trustee-Administrators’ Annual Report to the members, and at the Annual General Meeting of the Canadian Hemophilia Society in Halifax. We thank them once again because, without those “very special people who are personally dedicated” to bleeding disorders research, it would not have been possible.

We want to go behind the scenes to capture those stories of dedication, those caring and committed persons who “made it happen” in those early years and into the present. It is the story of our Nurse-Coordinator in Vancouver, Lois Lindner, who organized a group called Clam Chops to pool resources to buy a Voting Class Certificate when the first subscription was made available. This past year Clam Chops II has also come into being under her enthusiastic and dynamic leadership. The Edmonton Region was the birthplace of The Million Dollar Club and, together with the Manitoba and Quebec chapters, has been among the earliest and major supporters. Raising money is a “family affair” in the Poyser family with Ken’s father, Raymond, and Art Olson personally selling 5,000 colouring books during the big “blitz” a number of years ago. They still are in there “pitching” by selling entertainment books for the region, with money going to research. Darlene Poyser also did her part by raffling off or selling her knitted goods in malls. The Manitoba Chapter has always been the leader in fundraising among all the chapters within the CHS, going back thirty years to when the Kubins and Percy Smith started selling sweepstake tickets in Winnipeg in shopping malls and other public venues. The Chapter moved on very successfully to bingo events and was also instrumental in getting rights to the coloring book campaign that raised so much money for the Million Dollar Club. (This campaign was subsequently taken over by the national organization and later the Edmonton Region). Lynne Künin recalls the efforts to raise money through the sale of sweepstake tickets and the colouring books, as well as an unsuccessful attempt to sell shampoo and conditioner. Selling the giant colouring books became the rage across the country, which generated at least $200,000 for the Million Dollar Club directly, and other mon-

ey that flowed to the Club indirectly through chapter and regional contributions as a result of the sales. The Quebec Chapter, during Richard O’Shaughnessy’s presidency, had developed a sophisticated distribution system and rented a warehouse, permitting the chapter to donate $100,000 to the Club over a two-year period. The Chapter today still raises money for research through its annual golf tournament. In Toronto, Rosemary Jensen had a garage-full of the colouring books which she tried to sell with great enthusiasm but, somehow, two years later the garage still held more books than she wanted! What counts is not how many books were sold, but the spirit that motivated her efforts! It wasn’t just the large chapters that raised money for research. Saskatchewan, with its small membership, was able to buy three voting memberships! In New Brunswick, Normand Landry organized a network of friends and business acquaintances that raised over $6000 from the sale of colouring books. In Nova Scotia Kevin Duffy and Paulien Peters, during their presidencies, promoted the sale of colouring books so the chapter could purchase a certificate. A member of the chapter, who operated a rural gas station, used to declare a day a year in which proceeds went to hemophilia research! A few years ago the South Western Ontario Region presented a cheque in the amount of $50,000 to the Million Dollar Club, money contributed in large measure by its members through its annual November Appeal. The Region has a tradition of such support which hearkens back to the research undertaken by Doctors Inwood and DeVeber with regional contributions. The Ontario Chapter and its regions distinguished themselves particularly in the purchase of our most recent issue. It is the spirit and enthusiasm behind these efforts across Canada that matters and has brought us to this landmark and will propel us to even greater levels of achievement in the future! There are many other stories to be told, I’m sure, if we but knew about them, but we express our appreciation to all the sung and unsung heroes of our organization and beyond.

In the past year-and-a-half, our efforts to sell Voting Class Certificates far exceeded our expectations. We set an objective of selling 50 and had to go back to our voting members for approval to increase that number, which we now expect to reach at least 60. As well we have sold Non-Voting Class Certificates, Honorary Memberships, and have received

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Donations. To the Canadian Hemophilia Society, the chapters and regions, and the individuals who have supported us, we express our deepest gratitude. Our total endowment has now exceeded $1,200,000 and we expect to receive at least another $100,000 in the coming year. We are working towards an objective of growing the total endowment to at least $1,600,000 and we have asked the Canadian Hemophilia Society to help us accelerate the process by investing in the new endowment fund so it can be “put to work” at the earliest possible time and thereby provide a quick return on their investment. Longer term, we dare to dream of the day when the endowment will be $2,000,000 and the Canadian Hemophilia Society and the Hemophilia Research Million Dollar Club will be spending double the present amount on research! We acknowledge the following who have contributed to our current campaign:

**VOTING CLASS CERTIFICATES**

In Memory of Gregory Bott
c/o Frank Bott and Family

Canadian Hemophilia Society
Edmonton Region
Hemophilia Manitoba
Hemophilia Ontario
Central Western Ontario Region
Ottawa & Eastern Ontario Region
South Western Ontario Region
Toronto & Central Ontario Region
Nova Scotia Chapter
Quebec Chapter
Clam Chops II
Dr. Gerry Grove
Lois Lindner
Diane Rudd
George Stephenson
Cheong K. Tan
Jamie Hill
Audrey Irene Saigeon

**NON-VOTING CLASS CERTIFICATES**

Susan E. Anderson
Guy Godin
Jamie Hill
David Holmes

**CONTRIBUTORS**

Canadian Hemophilia Society
Hemophilia Manitoba

**DONORS**

Hemophilia Manitoba
Joan Fulton
Grace Jasper
Dr. David Lillicrap
Lolita Pelletier

The greatest challenge for the Million Dollar Club in the past year has been the continuing decline in interest rates. Because our investments are all in government and corporate bonds, we have seen a decrease in our net investment income from approximately $81,000 in 1999 to $65,000 in 2000. This situation will prevail until interest rates again move up to higher levels and/or we are able to get the new endowment to the point where its earnings can be used for current research. However, our return on investment has been higher than most funds that invested in equities. The market value of our portfolio (at the end of 2000) retained a healthy relationship to our total endowment, indicating that the fund is in good shape despite the volatility and uncertainty of the markets. While our major objective last year was to sell Voting Class Certificates (and they will be available to year-end), our emphasis this year is shifting to raising non-capital donations for current research while we continue to “grow” our total endowment.

The Hemophilia Research Million Dollar Club is the most effective way in which you can support bleeding disorders research in Canada. This is “our” fund, which is tangible and visible evidence of our commitment to research. Your financial support, whether you purchase a membership or make a donation, goes 100% to research (there are no administrative or fundraising costs) and is tax-deductible. In the past years the Million Dollar Club, in partnership with the Canadian Hemophilia Society, has provided funding for diverse research projects including Gene Therapy, Health-Related Quality of Life, Correction of Mutations, Blood Coagulation, Regulation of von Willebrand Factor Secretions, and many others. Never has the promise of research been greater! As Dr. Bruce Ritchie, Chairman of the Association of Hemophilia Clinic Directors of Canada said in the last Hemophilia Today, the next major advance in hemophilia care will be “gene therapy,” certainly the more imminent promise of improved treatment and eventually a cure. Why not “deal yourself in” and be a part of these developments?

For more information or to make a donation call/write to Joyce Gouin:

**Hemophilia Research Million Dollar Club**
c/o Canadian Hemophilia Society
625 President Kennedy, Suite 1210
Montreal, Quebec H3A 1K2
1-800-668-2686

We want to thank those who have given us their personal support. In particular, we gratefully acknowledge the never-failing endorsement of the Past President of the CHS, Erma Chapman, which meant so much to us and contributed to our success. We also want to thank the staff of the national office, who provide us with administrative support (at no cost to the Club). Very specifically we thank Daniel Lapointe the CHS Executive Director, and Joyce Gouin our staff resource person. I want to personally thank my fellow trustee-administrators, Daniel Baribeau and Lawry MacLeod, with whom it has been a pleasure working through the issues and challenges facing the Million Dollar Club in our two years of collaboration.

As is our commitment and tradition in the Million Dollar Club, we acknowledge annually in Hemophilia Today the Contributors (who have purchased Honorary Memberships) and the persons or groups they have honored. Many of these are no longer with us and are honored in memory, some of these and others still living are recognized for their achievements on behalf of those affected by bleeding disorders.

**CONTRIBUTORS**

Jeff Brownrig & Poyser Family
Canadian Hemophilia Society
British Columbia Chapter
Calgary Region
Edmonton Region
Hemophilia Manitoba
New Brunswick Chapter
Newfoundland Chapter
Nova Scotia Chapter
Prince Edward Island Chapter
Quebec Chapter
Saskatchewan Chapter
Hemophilia Ontario
Central Western Ontario Region
SERODISCORDANT COUPLES AND THE DESIRE TO HAVE CHILDREN:

a legitimate desire, but in Europe, not here

by Emmanuelle Simony, Member, Quebec Chapter

Do you know what a serodiscordant heterosexual couple is? It is a couple where only one of the partners is seropositive (infected with HIV). In couples where the woman is seropositive, the medical establishment has looked at the desire to procreate in order to reduce the mother-child transmission rate. Results obtained to date show a rate of about 1% in terms of mother-child transmission when the pregnancy is caught early. In the majority of serodiscordant couples where the man is seropositive, things are more complicated. This is the case with my husband and I, and many other people. Most of us are between 25 and 40 years old, i.e., at a reproductive age. And thanks to the increasing number of treatments, for most of us seropositivity has become a chronic, if sometimes abstract, condition in all cases under control. Our only remaining concern is not to infect our partner. However, using condoms means that we are sterile as couples. This creates a conflict between our wish to protect our partner and our desire to reproduce. In many cases, this very personal dilemma is solved by adoption, despite the attendant complications (officially prohibited in most countries for people infected with HIV). Others have taken the chance, through having unprotected sexual intercourse during the ovulation period, of trying to resolve this dilemma alone, with the serious risks associated with this decision.

Some have turned to donor insemination, but this solution does not necessarily meet everyone’s expectations. However, you should be aware that there are other options for couples like us, who should not be restricted to these difficult choices. For the past 9 years (since 1992), medical teams in Italy (Milan) and Spain (Barcelona) have been giving serodiscordant couples a chance to achieve their legitimate desire to have their own children under the safest possible conditions. These two teams have conducted about 2,500 insemination procedures so far, and not one single case of infection has been reported:

The AIDS virus is present in the sperm in different forms, i.e., in free form or incorporated in some cells. Some researchers think it could also adhere to the spermatozoa themselves, but there is no agreement in this regard and no study has been able to prove this hypothesis (the spermatozoid does not seem to be the HIV vector (carrier) in the sperm, and if it has any receptors, it seems to express them very weakly). Using a technique called “sperm washing,” originally used in infertility cases but which has been modified and specialized, the spermatozoa are isolated from the seminal fluid and other cells that may contain a viral particle (density gradient centrifugation technique, then washing and upward migration of the most mobile spermatozoa). “The protocols linking all these techniques lead to the elimination of the potentially infectious presence of leucocytes in over 99% of the final preparations.” A portion of the samples collected is frozen for insemination purposes and the remainder undergoes virological tests to verify the absence, below a detectable threshold, of HIV or the hepatitis C virus (viral DNA proviral genomic material and HIV RNA, HCV RNA). Although these techniques substantially reduce the risk of infection, because we cannot be sure they are absolutely risk-free, we have to look at what happens in practice. We find that, even if there is still a theoretical risk of a viral presence in the inseminated samples after washing, there have been no clinical cases of infection reported out of the more than 3,000 insemination procedures that have been done in Europe to date. Published scientific studies confirm that these techniques offer a safe alternative for reducing the risks.

Following these results, many other European countries made the procedures available in clinics or hospitals (4 centres in France, 1 in England, 1 in Switzerland and several in Germany). It is easy to get into most of them, and all the necessary preliminary examinations can be done here, which reduces the length of stay in a foreign country. The total price of an insemination procedure varies between $2,000 and $5,000 depending on

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In September 2000, the Canadian Hemophilia Society contracted with the Institute of Health Promotion Research at the University of British Columbia to conduct a psychosocial needs assessment of Society members. This nine-month study was conducted by Dr. Patrick McGowan, Assistant Director and Research Associate at the Institute. Dr. McGowan and his team of ten researchers used several research methods to investigate what was causing people emotional, social and, psychological stresses in the lives.

In this study of individuals with hemophilia or von Willebrand Disease (with or without hepatic C) a psychosocial need was defined as something that:

- may or may not exist;
- may cause "stress" in the individual and within his/her family;
- was brought about by past events, current living situations and circumstances, and by the larger environment; and
- may interfere with the process of managing one's health condition and having control over one's life.

It was important to hear the perspectives of all the stakeholders and therefore the study sought input from four groups.

The study team sought the opinions from:

1. Persons who were currently experiencing these conditions. This group included adults: a) with hemophilia; b) with hemophilia and hepatitis C; c) with von Willebrand disease; and d) with von Willebrand disease and hepatitis C.
2. Parents and caregivers of persons with these conditions.
3. Health Care Professionals. This group included those who work with persons with hemophilia, hemophilia and hepatitis C, and von Willebrand disease (e.g., physicians, nurses, social workers, and occupational therapists).
4. Policy and Planning Personnel. This group included board, committee, and senior staff members of the Canadian Hemophilia Society, and provincial chapter leaders.

As well, the study included a comprehensive literature review of over 100 published journal articles describing research on the psychosocial impacts of hemophilia, von Willebrand disease and hepatitis C. The information derived from this review augmented, clarified, and gave a more meaningful interpretation to the findings.

Research Methods

Five separate research studies (activities) were conducted:

1. A telephone survey with 51 persons with hemophilia only, 89 persons with hemophilia and hepatitis C; 27 persons with von Willebrand disease; and 10 persons with von Willebrand disease and hepatitis C.
2. A telephone survey with 71 parents and caregivers of children or young adults with these conditions.
3. Five focus group meetings with 48 Hemophilia Chapter or committee members. These meetings took place in five cities - Vancouver, Saskatoon, London, Toronto, and Montreal.
4. A Delphi Technique survey with 28 health care professionals (11 doctors, 9 nurses, 4 social workers, and 4 physiotherapists).
5. A literature review of publications since 1990 and other relevant materials on the psychosocial needs of the target populations.

Findings

The published literature on hemophilia consistently reported factors that bring about psychosocial stresses in persons with hemophilia. For parents these have usually included guilt, family planning, setting limitations on child's activities, and disclosure. For children they included anger, rebellion, pain, stigma, general anxiety, and low self-esteem. These psychosocial issues were also identified in the current study. For persons with hemophilia and also infected with the hepatitis C virus, the literature reported: uncertainty of the future, stigmatization, financial toll, the sense of hopelessness and despair, mistrust and anger towards the health care system, strained relationships with health professionals, anxiety, and depression. For persons with von Willebrand disease, the literature was sparse but did report concerns concerning fatigue, stigmatization, and issues around family planning.

This research study used different methods to obtain the opinions of persons in each stakeholder group (i.e., persons with these conditions; parents and caregivers; board, committee and staff members; health care professionals) in all provinces. The findings indicated there is a good degree of consensus regarding the things causing psychosocial stress. The following section provides a brief description of the major factors that brought about distress in adults experiencing these health conditions.

Concerns about the safety of blood products. There was an overwhelming feeling of fear regarding the safety of blood products. Participants were worried that those responsible for ensuring safety in the delivery of blood products may not be able to carry out this responsibility. Having experienced previous mismanagement, people still lacked confidence in the system. This fear was emphatically expressed in the focus group meetings, and health care professionals identified it as a common anxiety they saw in their patients. This concern was paramount because people still need to use the blood products.
Frustration with health professionals. This frustration was primarily directed at professionals working in hospitals (particularly Emergency Departments) and in the community offices. Generally participants were very satisfied with their health professionals providing specialized care in the hemophilia clinics. Persons with hemophilia and von Willebrand disease, and persons with hepatitis C expressed this frustration. People were mainly frustrated because they felt these hospital and community health professionals did not have the knowledge and expertise needed to deal with their problems. As well, there was frustration over the difficulty and complexity people experienced in obtaining a diagnosis, especially for von Willebrand disease. This concern was consistently identified by each stakeholder group as well as by the literature.

Uncertainty and fear of the future. This is a concern experienced by persons with hepatitis C and expressed by persons who participated in the focus groups, in the telephone surveys, and by health professionals. As well, this concern was identified in the literature review. People said they were afraid of losing physical and mental competencies and not being able to cope with problems they may experience in the future. Also, participants said that their concept of “future” had become blurred and uncertain, and they were unable to make commitments and plans because they weren’t sure what was in store for them.

Anger toward government. This feeling was particularly paramount in persons who had contracted hepatitis C. It was strongly expressed by persons in the focus groups, and observed frequently by health professionals in their patients with hepatitis C, and in the telephone interviews. The anger stemmed from the feeling that it was government policy and mismanagement that initially caused the hepatitis C infection, and that government was not taking its full responsibility to redress this situation. They were upset because: “government never even apologized for their action/inaction” and they feel that the onus of responsibility for care has been placed on their shoulders – the government was staying aloof. A number of people were angry because specialized hemophilia services were simply not available in their province (e.g., Saskatchewan) or in other specific geographic areas. Another aspect of this anger was the anxiety that government may not safeguard current levels of services and they may not be available when needed in the future.

Social Isolation. Persons, especially in rural areas, felt isolated and alone because they did not know other persons with similar condition(s). They felt alone and not supported because they did not have opportunities to share information and concerns with others. They felt a lack of social and peer support. Social isolation was also a feeling expressed by women with von Willebrand disease in that it was a relatively rare condition.

Impact on Career and Future Plans. Participants reported anger and frustration over limited career choices and how it had a negative effect on their lifestyle and financial health. They also described how they were not being able to accomplish all the things they felt they should have been able to accomplish, and the “unfulfilled roles” (e.g., being a successful breadwinner, being a grandfather, and being a coach) they have not experienced, and this fuelled feelings of “worthlessness” and of being unproductive.

Ongoing Emotional Strain and Exhaustion. Participants felt overwhelmed by the scope, complexity, and changing nature of the situation. They said they were: “sick and tired of being sick and tired.” They described the feeling as the cumulative effect of a series of losses and emotional strains that occur when a member of one’s family or community is sick or dying. People also said they were intolerant to everyday stresses because they were just exhausted and tired of always having to fight with health professionals, administrators, and teachers. Related to this feeling of emotional exhaustion was the feeling of constantly feeling fatigued that was expressed by persons experiencing hepatitis C.

Convergent Analysis

A needs assessment can identify unmet needs, but a more involved and comprehensive process is needed to prioritize findings and decide which action(s) needed to be initiated. These decisions also need to take into account the larger context of the organization and its current initiatives. This process is referred to as a “convergent analysis”. The need to ensure that this process would take place in the needs assessment study was identified in the early planning stages of the study, and a national project Advisory Committee was established to fulfill this role. Committee members included: Marc Laprise, Service Coordinator, Toronto Central Region, Hemophilia ON; Kelly Steiss, Regional Service Coordinator, Ontario, Hemophilia ON; Greg Taylor, Hemophilia Assessment Clinic, Vancouver BC; Angeliki Souranis, Regional Hemophilia Clinic, Montreal Children’s Hospital, QC; Patrick McGowan, Institute of Health Promotion Research, University of BC; Jean-Claude Boisvert, Canadian Hemophilia Society; and Robert St-Pierre, Hepatitis C Program Coordinator, Canadian Hemophilia Society.

All the information obtained from the stakeholders using the various research methods, as well as the information from the literature review, was synthesized and subjected to discussion and scrutiny by key members of the Hemophilia Society. Convergent analysis activities have already taken place on three occasions. As they became available, study findings were distributed to Advisory Committee members for review and feedback. The findings were also presented and discussed by the Hepatitis C Task Force in a meeting during February, and by Hemophilia Society staff and key Chapter members and staff at a Hemophilia planning meeting in March.

Dissemination

The final report of the needs assessment study was completed and is available from the Hemophilia Society. The findings are also available in several other ways:

- A 10-page report written in lay language for the general public;
- Ten 4-page Fact Sheets (placed on the Hemophilia Society’s web page) covering the following topics: Description of Research Methodology, Hemophilia Results, Hemophilia and Hepatitis C Results, Von Willebrand Disease Results, Von Willebrand Disease and Hepatitis C Results, Results of the Focus Group Meetings, Results of the Survey of Health Professionals, Results of Interviews with Parents and Caregivers, Summary of the Literature Review, and Summary of Results – all methods.
- A 50-page Report about the study and the findings.

In addition to these dissemination methods, Dr. McGowan presented the results at the First Canadian Conference on Hepatitis C in Montreal in May, and a research article describing the study and findings is being prepared for Haemophilia: The Official Journal of the World Federation of Hemophilia.
**All About Hemophilia**

**A Guide for Families**

For families dealing with newly diagnosed children with hemophilia, the utter shock and anxiety many parents feel can be overwhelming. Over time, families have their own experiences, meet other families and continue to learn about hemophilia. As our kids get older, we experience different types of bleeds, we see our kids struggle with anger and resentment and we eventually hope to see them accept hemophilia, but by no means to let it define them. Wouldn’t it be wonderful if a guide for families existed, that could help us all along the way?

It’s here, and it is called “All About Hemophilia: A Guide For Families”.

Over 25 writers have contributed to it, and even more families and kids have shared their thoughts, experiences and pictures with us. The English version of “All About Hemophilia: A Guide For Families” will be available across Canada by early December. One copy per family will be made available to you through your Hemophilia Treatment Centre. The French version will be available in the New Year.

I had the opportunity to be one of several parents helping with this project. What impressed me the most, is the amount of time so many team members put in and the incredible commitment from medical and non-medical volunteers across the country. “All About Hemophilia” reflects the collective perspectives and efforts of our community. We are living in a country where our kids have every reason to look forward to a bright and hopeful future. We have an outstanding team behind each and every one of them.

In 1993, “Hemophilia In Perspective” was published. It became our key reference guide and resource for care standards and information. It was a collaborative project- members of the Comprehensive Care Hemophilia Team at The Hospital for Sick Children, Toronto, parent volunteers and The Canadian Hemophilia Society. "All About Hemophilia" is the new and revised version of the original resource guide.

“All About Hemophilia” is also a collaborative effort. A national committee worked on this project including doctors, nurses, physiotherapists, and social workers from Hemophilia Treatment Centres across the country, parent volunteers, adults with hemophilia, and Canadian Hemophilia Society staff. Children, teenagers and parents have shared their thoughts on many subjects. Even pictures from kids and families across the country have been used in the new guide. The overall effect is a national focus, a personalized document and coverage of medical, emotional, educational and social issues.

In particular, there is more information on mild and moderate hemophilia, inhibitors, dentistry, teenage issues, and coping strategies for parents. Some chapters have been updated, some have been taken out and of course, new material has been added. The original binder format has been kept to enable removal of individual chapters for photocopying and distribution to family doctors and dentists, teachers, babysitters, friends and family members.

The layout and graphics of All About Hemophilia are fresh and user friendly. Chapters have been written in question and answer format to enable users to use the guide easily and to get to the information they need. Side bars in all the chapters include trivia questions, and quotations from kids, teenagers, doctors and parents. A reference system has been included to define terms and to provide cross references. Some subjects are covered in several places in the guide. There are various family perspectives as well to augment the medical information. A detailed resource list is included, listing current materials available from books to web sites. Contact information for all Hemophilia Treatment Centres and Canadian Hemophilia Society locations is there too.

The team behind this project includes many people who gave of their time, experience and expertise. The results are clearly evident in the comprehensive and dynamic nature of “All About Hemophilia.” Without the great team of volunteers who worked on this, it never would have come to fruition. We thank each and every one of you.

We would never have completed this project without the perseverance of 2 special people. Thank you, Clare Cecchini for rounding us up and pushing forward with our schedule of deadlines. A committee of busy people is so hard to steer. You did it with grace, and enough persistence to hold us all accountable. Thank you, David Page, our editor. Your knowledge and writing acumen are formidable. Your commitment to this project got us to the finish line. Bravo!

We hope you enjoy “All About Hemophilia: A Guide For Families”. Let us know what you think.

As always, be safe and be healthy.
Serodiscordant couples continued from page 21

the technique used (artificial/intra-uterine insemination or in vitro fertilization). In both cases, ovulation is induced by taking hormones. Artificial insemination consists of injecting the washed sperm in the uterus with a catheter, while in vitro fertilization consists of fertilizing the oocyte in the laboratory, then transferring the embryos into the woman. In North America, although medical professionals are familiar with these techniques, they are still not accessible to serodiscordant couples. For debatable ethical reasons, and because of legal fears and concerns about not intervening or taking sides, very real barriers have been erected between couples and their desire. On what grounds exactly should we still succumb to prejudices and conceal our situation?

Obviously, using these techniques does not automatically result in a pregnancy. The success rate varies, and you have to be prepared to undergo several insemination procedures. Therefore, it may be a long process, and although it is not painful physically, it may be difficult psychologically... as for any couple with fertility problems. Frustration and the waiting associated with this process should not be underestimated. However, there is a big difference between these feelings, which arise out of a personal, informed choice, and those generated by a lack of choice. When the medical profession does not pass on the information, when prevailing social pressure and the absence of debate prevents access to these options, when serodiscordant couples are thus forced to deal with imposed sterility or unnecessary risks, then we can talk about pain, anger and frustration.

For years we tried to obtain information and understand the options available to us. In the early nineties when we met, we spoke cheerfully about adoption. But at that time, we were too young to want children. So we started living together but always kept, deep inside, this hope of normalcy, like many other hopes. We did not count on the power of this feeling that gradually changed from a wish to a desire, then a need. Little by little, the barriers were falling: less social psychosis, greater access to the world work, availability of effective antiviral therapies... Then we resurrected our dream of having children, to complete the process of "healing the difference". This is when we learned we could not adopt. As a single woman, I could adopt, but as the wife of a seropositive man, I forfeited this right, which was out of our control unless we falsified our medical records. At this point in wondering what to do, we did not even think about donor insemination, but we had heard about what was happening in Europe. However, it was still at an embryonic stage and difficult to get. What mattered to us was that we were sure of our rights and therefore ready to do anything within the limits of our choices: having a child together under the safest possible conditions so that neither the baby nor I would be infected in the process. Since we were not prepared to take the chance alone, we turned to the doctors for assistance and to help us create what we thought was an ideal situation, i.e., respect for our decision and non-discriminatory access to medical care promoting our physical and psychological well-being.

And what were we told? That we were wrong, that we had no right to reproduce, that the only real solution available to us was not to have children. Let me make this quite clear: we were supposed to be satisfied with being alive and healthy and should stop making any more demands on life. To some extent, we had overlooked the AIDS since the only thing we had to live with was seropositivity, but we were reminded about it in no uncertain terms. But on what grounds? They talked to us about moral and ethical responsibility towards this new life. But where does the responsibility of the medical establishment lie when its passive refusal to help does nothing to reduce our expectations? Lack of assistance only increases the danger. They talked to us about the fear of infecting medical personnel, the theoretical risk of infection by insemination, and the lack of enough couples in our situation to make access to these techniques financially viable. They spoke the language of fear, avoidance and lack of respect, based on a rigid vision of AIDS. It is time to reconsider the evidence. Given the scientific facts, we can no longer talk only about the rights of couples but also about the duty of the medical community to help them. What other arguments still hold water? Which is why we went to Spain this summer. After lengthy discussions, we made the decision to take the time and mobilize all our financial and emotional resources to pursue our dream to the utmost. In doing so, we discovered another country and another culture, and we met a doctor who spoke the same language as us. How wonderful... I was inseminated twice. However, I am writing this article today not because I am pregnant – for "natural" reasons, the inseminations did not work – but because I was able to make the choice to try something which I was told was next to impossible. I am writing this article because I want to share this freedom and with my story change the situation in our country, at least that is what we can hope for.

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1 A French team followed couples who chose this technique. There were a total of 68 pregnancies and 4 cases of seroconversion. See Mandelbrodt et al., Lancet. 1997.
2 L. Bujan et al., Désir d’enfant et sérodifférence pour le VIH: Conseils et prise en charge.
3 Density gradient centrifugation technique: the sperm is put in a tube on top of different density solutions and spun in a centrifuge. The most mobile spermatozoids, which are the most likely to be healthy, separate from the seminal fluid and fall to the bottom of the tube, protected by the dense solution. As a second precaution, this layer of spermatozoids is washed and then put back in the tube, and another solution is added to which only the spermatozoids will migrate; only the upper fraction which contains the most mobile spermatozoids is kept.
6 In France, the results of the Toulouse Protocol in July 2001 were as follows: 116 insemination cycles, 20 pregnancies (success rate of 17%); the success rate of the Spanish team was between 11% and 25% by intra-uterine insemination and from 17% to 46% by embryo transfer. However, the figures vary depending on the procedures, ovulation stimulation treatments and AMP techniques used.
ReFacto™ Close to Approval in Canada

Kogenate®FS, Helixate®FS and Recombinate® are well-known concentrates to many Canadians with factor VIII deficiency. Now, a fourth product, ReFacto™, already licensed for use in Europe and the U.S., is close to approval by Health Canada. To find out about this treatment for hemophilia, Hemo Today interviewed Jay Feingold, MD, PhD, who is Director of Hematology and Oncology, Global Medical Affairs at Wyeth/Genetics Institute; and Rod Miller, B.Sc, B.A, who is Business Unit Manager, Specialty Business at Wyeth/Genetics Institute in Canada.

Hemo Today: Please describe the history of the development of ReFacto™.

Jay Feingold: Wyeth/Genetics Institute has a strong heritage in the hemophilia marketplace. We were the first company to discover and clone recombinant factor VIII and factor IX. ReFacto™ was first developed in the mid-1990s by Pharmacia and Upjohn, a Swedish pharmaceutical company. In 1997, Wyeth/Genetics Institute, which already manufactured recombinant factor IX, entered into a development and commercialization agreement with Pharmacia and Upjohn whereby Wyeth/G.I. took control of future development and most marketing of the factor product. Currently, we are the only company to have recombinant products for both Hemophilia A and B, and the only company that manufactures exclusively recombinant products.

Hemo Today: ReFacto™ is special in that its factor VIII molecule is missing the B-domain. Could you explain in simple terms what this means?

Jay Feingold: The factor VIII molecule is made up of several large sections, each one called a domain. It was found that the B-domain did not play a role in blood coagulation. So when ReFacto™ was developed, it was decided to design a molecule in which the B-domain was deleted.

Hemo Today: Does the fact that the B-domain is missing have any effect, either positive or negative, on its ability to stop bleeding in people with hemophilia?

Jay Feingold: No, it doesn’t. ReFacto™ has been found to be effective in a variety of situations, including those involving surgery. In studies with a large number of patients over several years, it has proven to stop bleeding in people with hemophilia. Its efficacy is comparable to other plasma-derived and recombinant factor VIII products.

Hemo Today: It was initially hoped that the ReFacto™ molecule, because it was missing the B-domain, would be less immunogenic, in other words that fewer people would develop an inhibitor to factor VIII. Has this turned out to be the case?

Jay Feingold: No, there is no sign of that. It is true that at the beginning of the development of ReFacto™, it had been hoped that the deletion of the B-domain might mean that fewer patients would develop inhibitors to factor VIII. However, in practice, we haven’t seen that.

Hemo Today: What have the studies shown with regards to inhibitor development?

Jay Feingold: Again we have seen results very similar to those with other factor VIII preparations. In the clinical studies, one of 117 PTPs (previously treated patients) developed an inhibitor. 32 of 101 PUPs (previously untreated patients), developed inhibitors during the clinical study. Sixteen of these inhibitors were high titer. The sixteen others were low titer. This percentage is similar to that seen with other factor VIII concentrates.

Hemo Today: Being a smaller molecule, is ReFacto™ easier to manufacture? And if so, does this mean that it will become available to people with hemophilia in higher quantity and at a lower price in the future?

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consisting of educational sessions and supervised fun activities, were planned for those under the age of eighteen. When registration kits went out the response from both provinces was overwhelming! 150 people attended with equal representation from both Saskatchewan and Manitoba. Not only were those with bleeding disorders and their families there, but hemophilia medical staff from both provinces were present. It was an especially profitable time for those from Saskatchewan, as three new clinic staff attended. This weekend gave the clinic staff a wonderful opportunity to meet many Chapter members, and to meet their counterparts from Manitoba. As well, we were honoured to have CHS President, Mr. Tom Alloway, as a special guest and session presenter at the retreat.

Elkhorn Resort was an outstanding facility and the surrounding National Park was incredible—people were very pleased! Elkhorn was quite a distance for some of those from Saskatchewan, 7 hours for some, but everyone said it was worth it. After the information sessions, there was plenty of time for participants to visit nearby Clear Lake and the town of Wasagaming, or to swim, play golf, or just relax. Other than one very brief thunderstorm the weekend weather cooperated wonderfully.

It is important to note that the retreat was made possible by the generous unrestricted financial support of Aventis Behring, Bayer, Genetics Institute, and Novo Nordisk. Representatives from the four companies who attended the retreat were able to witness for themselves the positive results of their support of the hemophilia community. Special thanks to Mark Wiener, Joanne Ukno, Guy Larente, and Dave Croft, for their enthusiastic support of the project.

As with any event, it takes time for people to mingle and feel comfortable with one another. But by the end of the weekend, both adults and children had made new friendships, exchanged valuable information, and went away encouraged. For the organizers, it was exciting to watch sixteen months of planning become reality right before their eyes. This Manitoba/Saskatchewan family retreat owes its success to all the participants who came together in such a generous spirit of “Growing Through Sharing.” It was a memorable weekend for all.

**HEMOPHILIA SASKATCHEWAN’S OPEN HOUSE – OCTOBER 17, 2001**

On October 17th Hemophilia Saskatchewan officially opened their new office. The Open House was well attended by more than 60 people. In fact, people even moved out into the hallway during part of the evening! Eric Stolte, V.P. International Projects, CHS gave the opening remarks; Faye Katzman, Hemophilia Saskatchewan president dedicated the office “to those who have gone before”; The Honourable John Nilson, Health Minister then presided over the ribbon cutting ceremony with one of our young hemophilia boys, Wade Penner.

One of the founding members of Hemophilia Saskatchewan, Lisle Spence, was present and was introduced. He commented that “things certainly have changed since they began around his dining room table with 5 people in 1965!” Indeed, dedicating the office “to those who have gone before” was very appropriate.

Clinic staff, both past and present, attended. Enthusiasm and excitement about our new office was contagious. The Health Minister spent about 2 hours mingling and talking with those who came. Since the House was sitting, one of our MP’s sent a delegate, and one of our MLA’s attended. There is certainly a heightened awareness of Hemophilia Saskatchewan’s presence in our province. The future is ours!
International Projects Update

China is a vast country both geographically (3rd behind Russia and Canada) and regarding its population (1.2 billion and growing at an annual rate of 12 million per year!). Helping to influence the quality of care in such a country is overwhelming, but this hasn’t stopped Dr. Man-Chiu Poon from beginning by setting up a clinic twinning between the hemophilia treatment centre in Tianjin (near Beijing) and Calgary. Then he was influential in getting another clinic twinning started between Dr. Luke in Ottawa and the centre in Guangzhou, the gateway to southern China. Exciting first steps in this vast country.

Recently, Dr. Poon applied to the International Projects Committee for funding for him and Dr. Luke to visit the hemophilia centres and associated facilities in Shanghai and Tianjin, China following their November meeting in Guangzhou. This will give them the opportunity to discuss how best to network the several hemophilia centers in China and to promote collaborative projects among these and other Chinese Hemophilia Centres. The web of help is beginning to spread from Tianjin to Guangzhou to Shanghai to…?

In early October Faye Katzman, President of Hemophilia Saskatchewan, Dr. Sheila Harding, a hematologist who works with Dr. Robert Card, Director of the Bleeding Disorders Program in Saskatchewan, and myself completed a First Assessment visit to Mongolia (see related article). We’re putting together a report of our visit, and then will be creating, in collaboration with our Mongolian friends, an Action Plan. This will be submitted to the World Federation of Hemophilia and, upon their approval, we’ll become an official twinning venture. Two of the three delegates were funded through the WFH after the visit was formally approved. One was funded through the Saskatchewan chapter upon obtaining a grant from Bayer. I felt that having a threesome comprised of two lay people and one doctor was an ideal team.

I’ve heard of interest in other twinning initiatives through other Canadian chapters. If you have an interest, please don’t hesitate to contact myself or WFH directly. There are countries that WFH feels are ideal candidates for twinning. If you’re thinking of a twinning possibility, the particular country of interest may or may not be a good candidate. The reason for the WFH funding a First Assessment visit is that not all twinning prospects work. It’s better to conduct a fact-finding trip to see if twinning will work than to enter into a twinning relationship only to find that, three to five years later, this wasn’t such a good idea. The WFH team who helps with this are invaluable partners.

There is still ample funding available from our CHS International Projects Committee for special initiatives that enhance WFH approved twinning opportunities. We also wish to resource chapters and regions as they consider twinning possibilities. We’ll look forward to hearing from you!

First Assessment Trip to Mongolia

Break, austere and unforgiving describe the image I have when looking down from 30,000 feet over Mongolia. The flight from Beijing to Ulaanbaatar, the capital and centre of Mongolia, passes over the Gobi dessert. 2.5 million people carve out a living in a land the size of Ontario and Quebec sandwiched between Siberia and China. With only 1-2% of the land arable and 50% of the population rural and nomadic, this is a challenge. Set free from the communist USSR in 1990, Mongolians have struggled to return to a life of comparable quality since then.

Dr. Sharav has been helping to treat hemophilia over a long time. As Chairman of the Coordinating Committee, he serves a vital role in linking the MAH to other health care officials and people who can provide resources. Unlike many of his colleagues of similar age and stature, he has a humble and sacrificial heart. Through his influence, we had a meeting with the Director of the Division of Policy Implementation and meetings with hemophilia treaters, doctors, health officials, the Red Cross Director, lab personnel and Medical School officials in Ulaanbaatar, the capital and population centre (700,000) of Mongolia. As if that wasn’t enough, we also flew by local airline to the capital of Huvsugul province, Murun, and then eight of us went via four person jeep to a small town, Bayan, a 1.5 hour drive away over the Mongolia “outback.” There we observed the treatment people with bleeding disorders receive away from the national centre. What we saw and heard reminded us of the state of treatment here about 50 years ago!

If you’re born with severe Hemophilia in Mongolia it’s almost guaranteed that you won’t see your 20th birthday. Mandaa, mother of six year old Enjig, looks across the room at Battayer, a 26 year old hemophiliac with a glass eye, two major broken bones never set correctly, crippling arthritis in several joints who suffers from occasional seizures, all from complications resulting from his hemophilia. Without improved care, she is looking at an image of her son 20 years hence. It’s no wonder Mandaa quit a good paying job to stay home and care for young Enjig. It’s also no wonder that she is part of the Coordinating Committee of the Mongolian Association of Hemophilia (MAH).

Formed only about two years ago, the MAH is comprised of both lay and professional people. Our primary host, Bileg, is a gift to the MAH. Although he has no personal association with Hemophilia, he knows the sister of a hemophiliac who recruited him to assist. Bileg has a large heart of compassion and concern for his people. He has sacrificed opportunities to live outside Mongolia so that he can be there to help. His language skills alone (he speaks Mongolian, English, Russian and Japanese) are a great asset. But even more is his commitment to help the bleeding disorders community by investing many hours as a volunteer.

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Coordination in the Mongolian Ministry of Health, Dr. Erkhembaatar. During that meeting, Dr. Erkhembaatar pledged to provide the MAH with free translation of educational materials and free national distribution of those materials. Dr. Sharav, too, is a gift to the MAH.

Heart-wrenching images remain etched into my memory. While in Murun, a family of six travel six hours (120k) to see us hoping that we might offer some kind of help. Also, the image of Namnangarau, a 20 year old hemophiliac also in Murun crippled by poor treatment who was unaware that he should at least ice his bleeds. Doctors telling us that they use whole blood transfusion to treat bleeds. Labs full of nonfunctioning donated equipment like the five of six refrigerated centrifuges in the blood product lab because the donors didn’t include manuals, support materials, spare parts or technical help. The reports of children who, after being diagnosed with hemophilia are never seen again probably because they died at home where there is no record of their death.

But there are also heart-warming images. The meeting with about 20 people, hemophiliacs and their families, in Ulaanbaatar eager to help and learn how to help themselves. Dr. Sheila Harding helping to diagnose a probable vonWillibrands previously unknown in Murun. Faye Katzman and Bileg, arms outstretched through a hole so technicians can take their donation of blood. The eager welcome and sacrifice of so many of the committee members and doctors. Hemophilia treaters and lay persons working on a Mongolian version of the acronym, RICE (Rest, Ice, Compression, Elevation) so that both treaters and families can decrease the severity of and damage from bleeds.

At the Farewell Dinner where we shared both a meal and gifts with the Coordinating Committee, there is one memory that particularly stands out. After Dr. Harding finishes taking some afternoon meeting with the families—Dr. Sharav makes a closing comment. “Before your visit I treated patients,” he said, “Now I will treat families”. I believe this is called a “paradigm shift.” I have little doubt that Dr. Sharav will share this with his colleagues. This alone will usher in better care for people with bleeding disorders in Mongolia.

Our next goal is to develop an action plan with the MAH and submit it to the World Federation of Hemophilia. Once approved, we’ll become an official twin. This particular twinning should work well because the MAH doesn’t need very sophisticated help and Hemophilia Saskatchewan is not a very sophisticated chapter. But over the years we’ve had an active and committed volunteer involvement. This is exactly what the MAH needs if it is to be effective in bringing change in the care and treatment of people with bleeding disorders in Mongolia.

Even if this trip doesn’t result in a twinning arrangement, it was worth it to see what a privileged place we have here in Canada. We have so much, not in the least due to our hard work to ensure that care. There is a saying that goes, “To whom much is given much will be required.” We, particularly in light of the level of care we enjoy, have a responsibility to offer what we can to those who have need. In that offering, both the receiver and the giver are enriched. I’ve already been enriched through our contact with the MAH. I’m hopeful that in coming years all of our Canadian chapters, as well as CHS nationally, will do what we can to help improve care for people with bleeding disorders in many parts of the globe.
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Jay Feingold: ReFacto™ is not necessarily easier to manufacture so I can’t say that it is really more economical to make. However, the absence of the B-domain of the molecule has meant that the product does not require the addition of albumin as a stabilizer in the final formulation. This is contrary to first-generation recombinant factor VIII preparations.

Hemo Today: Many consumers are still concerned about the presence of human proteins, specifically albumin, in factor concentrates. Does ReFacto™ add albumin to the cell culture used to multiply the molecule?

Jay Feingold: ReFacto was the first recombinant factor VIII product with an albumin-free final formulation to gain U.S. FDA approval. Our process still requires the addition of human albumin to the cell culture at an early stage of manufacturing. Wyeth/Genetics Institute uses the safest albumin source we can find. ReFacto™ then goes through a process which includes a solvent detergent step and multiple chromatography purification steps. As a result, albumin cannot be detected in the final product. Although there may still be traces of albumin, there is so little it cannot be measured. Additionally, the purification process includes the use of a mouse monoclonal antibody and the protein is initially expressed in hamster cells. Even though no mouse or hamster proteins are detected in the final ReFacto™ product trace amounts could theoretically be present.

Hemo Today: You mentioned that albumin is not used to stabilize ReFacto™ in the final preparation? What is the stabilizer?

Jay Feingold: The incipients in the final formulation of ReFacto™ are sucrose, polysorbate 80, L-histidine, sodium chloride, calcium chloride (dihydrate) and sterile water.

Hemo Today: What is your evaluation of the risk of this residual albumin with regards to prion contamination? (Editor’s note: Prions are misshapen proteins believed to be the cause of Creutzfeldt-Jakob Disease and variant Creutzfeldt-Jakob Disease (vCJD). While no case of either disease is ever known to have been caused by blood or blood products, the theoretical risk of transmission remains a concern.)

Jay Feingold: We would all like to move towards a product which has no exposure to human or animal proteins. I was doing my hematology fellowship during the 1980s which was a very difficult time for the hemophilia community. So I understand the concerns. However, if I were a parent of a young child with hemophilia today, I would be very comfortable with the safety of today’s recombinant products.

Hemo Today: Are there any plans to develop a next-generation ReFacto™ product without albumin in the cell culture?

Jay Feingold: Yes, Wyeth/Genetics Institute is well-advanced in the development of a third-generation recombinant factor VIII which does not use any human or animal proteins at all during the manufacturing process, similar to our factor IX product, BeneFIX®. We are not far from beginning clinical trials.

Hemo Today: What is the licensing status of ReFacto™ in some of the major markets around the world, that is, U.S., Europe, and Canada?

Jay Feingold: ReFacto™ was licensed for use in Europe in 1999 and in the U.S. in the first quarter of 2000.

Hemo Today: When do you expect ReFacto™ to be licensed in Canada?

Rod Miller: Wyeth/Genetics Institute submitted ReFacto™ in 1999 to Health Canada for regulatory approval. The ReFacto™ file is under active review by Health Canada and we expect to receive a Notice of Compliance from Health Canada in the last quarter of 2001 or very early in 2002.

Hemo Today: What position has Canadian Blood Services (CBS) taken with respect to covering the cost of ReFacto™ in Canada?

Rod Miller: I am unable to speak for the CBS directly but can assure readers that we are proactively working with them to secure funding for ReFacto™ to support commercialization in Canada. We fully expect that ReFacto™, like other recombinant factor VIII products, will be made available to Canadians in the near future.

Hemo Today: Factor VIII concentrates, and particularly recombinant factor VIII concentrates, have been in short supply in the world over the last 8 months, in part due to increased demand, and in part due to manufacturing problems at certain suppliers. What is Wyeth/Genetics Institute doing to alleviate this problem?

Jay Feingold: Wyeth/Genetics Institute remains strongly committed to increasing the supply of ReFacto™, and we continue efforts to increase production capacity through manufacturing expansion projects. Wyeth/Genetics Institute has built a second ReFacto™ manufacturing facility in St. Louis, Missouri. We expect to receive U.S. and European approval to start distributing product from that facility in the first half of 2002. Combined with our existing plant in Stockholm, we will be able to increase our annual recombinant factor VIII production by three- or four-fold. This will help in alleviating some of the current shortages.