Bleeding and Clotting Disorders

Introduction

The primary mission of the Hematologic Diseases Branch (HDB), DASTLR, is to reduce the complications of hemophilia and other bleeding and clotting disorders. To fulfill this mandate, the Branch has instituted a multidisciplinary research approach which includes surveillance, health education, coordinated prevention and intervention activities for health-care providers and lay populations, and epidemiologic and laboratory research directed towards providing a developmental basis for intervention activities. Drawing on each discipline, the Branch sets national goals for preventing complications associated with bleeding and clotting disorders. Currently, the Branch is focusing on three national goals: 1) enhancing blood safety for clotting factor to prevent the transmission of infectious disease to persons undergoing treatment for bleeding disorders; 2) eliminating and/or reducing joint disease among persons with hemophilia; and 3) reducting morbidity associated with bleeding disorders among women. To accomplish these goals, the Branch participates in health-care intervention programs for hemophilia treatment centers (HTCs) and the lay community, as well as epidemiologic and laboratory research to establish prevention efforts in hemostasis and thrombotic diseases. Program effectiveness is determined by outcome measures analyzed by Branch surveillance, epidemiologic, and laboratory teams which are stated here as accomplishments then translated into new goals for the next year.

1999 Accomplishments

Surveillance Activities

- Refined surveillance instrument utilizing all investigators involved in the Hemophilia Surveillance System (HSS), which monitors the complications of hemophilia among patients receiving treatment within and outside HTCs in six states funded through cooperative agreement (Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma). Data reviewed from the first 4 years of the project indicated a need to modify data collection tools to clearly survey blood-borne infections among study participants. In the fifth year, project sites implemented the modified surveillance tools and final data collection and analysis on blood-borne infections continues through FY 2000.

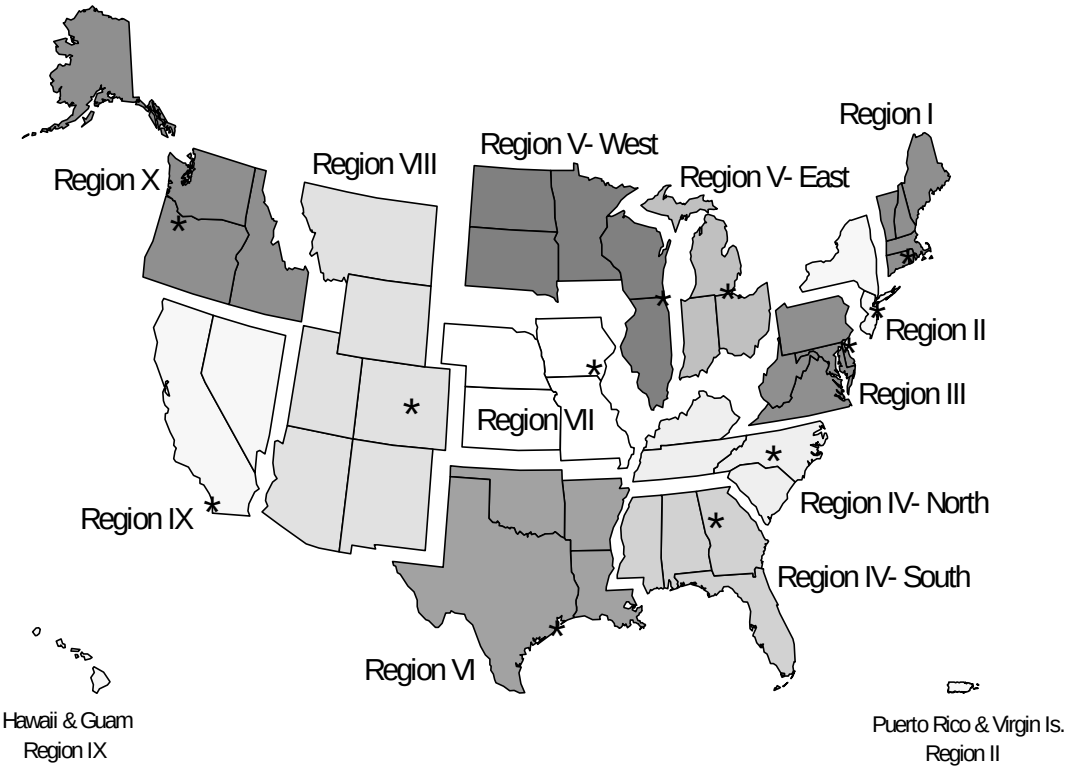
  In 1999, the final phase of HSS began. Data from this first population-based study of hemophilia in the United States resulted in determining the occurrence of hemophilia in six states and estimating the size of the national hemophilia population. Data indicate a very significant reduction in mortality and hospitalization rates among patients participating in CDC's HTC prevention programs. In addition, data analyzed in 1999 provided additional information regarding severity of joint disease among persons with hemophilia and the incidence of infectious disease and intercranial hemorrhage among this population. This information is translated to CDC prevention, intervention, and educational programs for patients and providers.

- Continued implementation of the Universal Data Collection (UDC) plan, which began in May 1998 as a phase-in process. Given available resources, progress in implementation has been excellent. Since May 1998, more than 5,000 patients have enrolled, representing more than 115 of the 134 federally funded HTCs across the country. The rate of invited participation among persons receiving care in HTCs has also been excellent (> 90%). We anticipate UDC enrollment of 9,000 – 12,000 patients with hemophilia and other bleeding disorders. Information obtained through UDC on blood safety, hepatitis vaccine administration, and joint mobility are used to improve CDC prevention, intervention, and education programs.

- Continued the surveillance in HTCs for the identification of possible Creutzfeldt-Jakob Disease (CJD) among persons with hemophilia. To date, no cases of CJD have been detected.

- Initiated the Central Venous Access Device (CVAD) study with the University of California at Davis for surveillance of complications associated with catheter or port device implants for transfusions among person with hemophilia.

Hemophilia Treatment Center Regions



Epidemiology/Laboratory Investigations

Women with bleeding disorders

- Completed data analysis from the study of the development of thrombosis during pregnancy. Manuscript accepted for publication in the *American Journal of Obstetrics and Gynecology*.

- Completed study of the maternal hemostatic system and recurrent fetal loss.

- Continued a collaborative study with the University of Medicine and Dentistry, New Jersey (UMDNJ), University of Louisville, and the University of Utah to examine the relationship between mutations in the maternal coagulation system and the birth of infants with intrauterine growth restriction (IUGR).

- Developed protocols in collaboration with four regional HTC sites for data collection related to the incidence and complications of bleeding disorders among women to determine the occurrence of underlying genetic abnormalities (i.e., von Willebrand Disease) as cause for these clinical manifestations in reproductive-aged women.

- In collaboration with UMDNJ, continued a project to test the usefulness of a questionnaire as a screening tool for inherited bleeding disorders in women with menorrhagia.

- Initiated and began development of a multi-site (Emory University, University of New York at Rochester, Mayo Clinic, UMDNJ) study of treatment and management of women with bleeding disorders.

Hemophilia

- Conducted a Hemophilia Genotyping Workshop with the National Heart, Lung, and Blood Institute (NHLBI).

- Identified a relationship between severity of hemophilia and the absence of Factor V Leiden.

- Initiated gene discovery studies using high performance liquid chromatography (HPLC)-based detection systems.

Myocardial infarction / venous thrombosis

- Conducted an investigation to identify a candidate gene involved in coronary artery disease.

- Continued a follow-up to the Legg-Perthes study to examine the genetics of protein C and

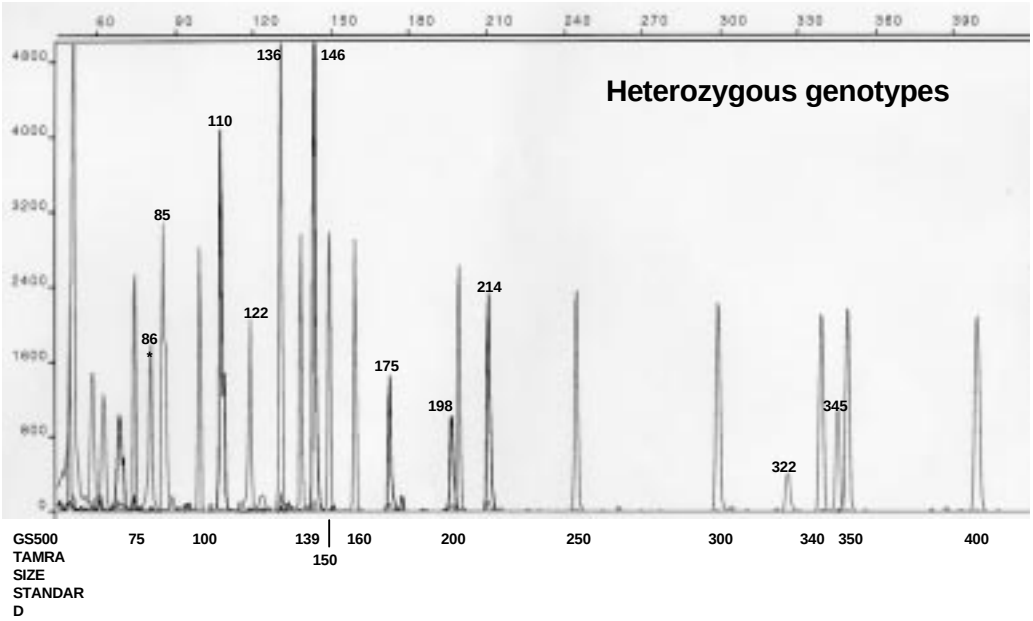
protein S in families with a history of Legg-Perthes disease.

- Continued a study of genetically abnormal clotting factors and the development of thrombosis during pregnancy.
- Continued case series to investigate the relationship of genetically abnormal clotting factors to necrotizing enterocolitis (NEC).
- Continued screening genes that may have predictive value for stroke in patients with sickle cell anemia.
- Continued a study to determine the distributions of plasma coagulation factors among African-Americans.
- Determined that ACE DD genotype is associated with both weight and blood pressure reduction in elderly white males but not among white females or African-Americans.
- Implemented a fluorescence-based detection system for high throughput gene detection.

Four SNP Assays in a Large Population Study

SNP	Codon	Nucleotide
Factor V Leiden	R506Q	G1691A
MTHFR	A222V	C677T
Prothrombin	3' untranslated	G20210A
HR2 Allele	H1299R	A4070G

Electropherograms following GeneScan® fragment analysis of four loci which were co-loaded



- In collaboration with Emory University, continued a study of genetic characteristics, coagulation activity, and levels of clotting proteins in the etiology of venous thrombosis in a population of whites and African-Americans (Genetic Attributes and Thrombosis Epidemiology Study or "GATE" Study). Completed genetic analysis of more than 300 subjects.

- In collaboration with Emory University, initiated and began development of a study of viral and genetic characteristics in the etiology of myocardial infarction in a population of whites and African-Americans (Genetic and Viral Attributes of Myocardial Infarction or GAVAMI). Completed questionnaire for investigation of the potential relationship between cytomegalovirus (CMV) infection and genetic risk factors for myocardial infarction.

- Initiated and began data collection for large cohort study in collaboration with Kaiser Permanente and the Scripps Institute to study the relationship between coagulation genes and development of thrombosis (Thrombosis and Genes Study or "TAG" study). An excess of 1,200 subjects have been analyzed for eight different genes.

Public Health Translation

- Collaborated with the National Hemophilia Foundation (NHF) in finalizing telephone interview data to identify areas for behavior change and to develop prevention messages for persons with bleeding disorders.

- Collaborated with NHF's Physical Therapy Working Group to establish a training process and verify skills to enhance the quality of data collection through UDC.

- Coordinated collection and summary of national Hemophilia Data Set to characterize patient populations utilizing the network of federally funded HTCs.

- Developed a marketing plan for HDB surveillance activities by: 1) reviewing existing educational materials; 2) conducting formative research to identify patients', families' and providers' motivations and barriers to participate in the surveillance activities; 3) designing educational messages according to the result of the formative research; 4) determining appropriate channels to distribute these messages; and 5) developing publications and other educational materials with a consistent theme and appearance.

- In collaboration with NHF and its consultants, completed a sampling design and protocol and initiated administration of telephone interview questionnaires for adults and youths with hemophilia or parents of children with hemophilia to: 1) measure compliance with a set of recommended prevention behaviors; 2) determine perceptions and actions related to use of HTCs; and 3) assess capacity for self-management of hemophilia.

- Maintained a national HTC directory to disseminate information to all or subsets of

hemophilia care providers by discipline.

- Participated in inter-center meetings to revisit CDC guidelines regarding safe conception among HIV discordant couples, including the appropriate use of assisted reproductive technologies. Conducted needs assessment among HTCs which had pregnant patients during the past year to assess interest among patients.

- Participated in 10 regional meetings of HTC providers to obtain input and discuss branch surveillance activities.

- Participated in NHF's Women's Task Force to provide input to national program planning and public awareness for women with bleeding disorders.

- Provided ongoing technical assistance to regional coordinators, including coordinating meetings for regional coordinators and directors.

Training/Education

- Created and published newsletter to provide exchange of information among HTCs participating in UDC.

- Developed a display highlighting CDC's activities in the bleeding disorders community for exhibition at NHF's annual meeting.

- Initiated a pilot study of a basic concepts manual for families of persons newly diagnosed with bleeding disorders; developed a pilot testing process and selected participants.

- Provided support to NHF for *HANDI*, the information service that provides information, resources, and referrals on bleeding disorders to affected families and their health care providers.

- Provided updates on blood safety and complications of bleeding and clotting disorders through a variety of regional, national, and international meetings of health care providers and lay community members.

Plans for 2000

Surveillance Activities

- Phase out HSS project, and continue expanded surveillance through UDC. Publish quarterly surveillance reports based on data from UDC.

- Continue surveillance system for the identification of possible CJD among persons with hemophilia to all 140 HTCs.

Epidemiology/Laboratory Investigations

Women with bleeding disorders

- Analyze data and publish findings from the study of the relationship between the maternal hemostatic system and recurrent fetal loss.

- Complete development of a multi-site (Emory University, University of New York at Rochester, Mayo Clinic, UMDNJ) study of treatment and management of women with bleeding disorders.

- Continue collaborations with UMDNJ for data collection to study the effectiveness of a screening tool to detect bleeding disorders in women with menorrhagia.

- Continue to provide technical and laboratory support to UMDNJ, the University of Louisville, and the University of Utah for the data collection phase of the study of the relationship between mutations in the maternal coagulation system and the delivery of IUGR infants.

- Submit publications from analysis of the study of von Willebrand disease and menorrhagia in reproductive-aged women.

Hemophilia

- Investigate the utility of HPLC-based detection methods for hemophilia genotyping.

Myocardial infarction / venous thrombosis

- Analyze data and prepare publication from the study examining the genetics of protein C and protein S in families with a history of Legg-Perthes disease.

- Analyze initial data and prepare initial publication for the TAG Study.

- Begin characterization of cardiovascular associated genes in a large, HMO-based cohort.

- Begin gene chip technology for hemophilia genotyping and new gene discovery for thrombosis.

- Complete development and begin data collection for study of viral and genetic characteristics in the etiology of myocardial infarction (GAVAMI).

- Complete the case series of the coagulation system and NEC in infants.

- Continue collaboration with Robert Wood Johnson Medical School to identify genes that may be associated with hypertension.

- Continue to investigate the role of APC in cytokine regulation.

- Continue to provide technical and laboratory support to Emory University for the data-collection phase of the GATE study.

- Continue to investigate gender-based genetic differences with respect to genetic risk factors associated with cardiovascular disease.

- Identify genes that may be associated with ischemic stroke.

- Initiate a collaborative effort with Harvard University to define the relationship between polycystic ovarian disease and cardiovascular disease-associated risk factors.

- Provide technical assistance and collaboration to investigators from Emory University to analyze and publish data from the study of genetically abnormal clotting factors and cryptogenic stroke.

Training/Education

- Analyze data collected on women treated at HTCs for von Willebrand disease to determine patterns of referral to HTCs, perceived treatment practices, and level of satisfaction among these women.

- Collaborate with NHF to analyze data collected through telephone interview to identify areas for behavior change and development of prevention messages among persons with hemophilia

- Continue to publish and disseminate a newsletter for HTCs to provide technical assistance and successful strategies for implementation of HDB's surveillance activities.

- Enhance HDB web page to provide forum for dissemination of information including surveillance reports.

Public Health Translation

- Continue to collaborate with NHF to identify targets for prevention messages related to bleeding disorders among women.

- Continue to develop Internet interactive data collection for HTCs in order to provide site-specific data to collaborators at each federally funded HTC.

- Define prevention messages for reducing bleeding disorder complications among women.

- Develop and pilot-test data collection projects to determine public health perceptions of thrombophilia. Utilize data to warrant activities for surveillance of thrombophilia in multi-disciplinary medical practice facilities such as HTCs.

- In collaboration with other federal agencies, explore opportunities for professional training programs for hematologist to address the imminent shortage of health care providers in federally funded HTCs.

- In collaboration with NHF, analyze telephone interview questionnaire data collected from 450 patients with hemophilia. Organize and disseminate data interpretations to the hemophilia community.

- Participate in three regional conferences providing training to prevention education teams designed to deliver prevention messages to persons with hemophilia.

- Through outreach programs initiated at the HTC level, expand disease intervention and prevention services to non- and under-served bleeding disorder populations.