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NHF e notes

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

A MONTHLY ONLINE NEWS BULLETIN SEPTEMBER 2003

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MEDICAL NEWS

SPECT Imaging may Replace Liver Biopsies in HIV/HCV Coinfected Patients

September 3, 2003

SPECT imaging may offer a noninvasive alternative to liver biopsies in HIV patients with hepatitis C. Performing a liver biopsy in patients infected with HIV and hepatitis C virus (HCV) is considered the standard of practice to assess hepatic involvement but carries risks to patients, sources explained. With this in mind, B. Shiramizu and colleagues at the University of Hawaii conducted a study "to identify single photon emission computed tomography (SPECT) parameters that correlate with liver disease stage."

"HIV-coinfected and HCV-coinfected individuals undergoing a liver biopsy had a SPECT scan performed," they noted. "The results showed that a number of SPECT parameters were associated with histologic changes in architecture, fibrosis and cirrhosis, of which two SPECT parameters, the minimum pixel count for spleen region of interest and maximum pixel count for right hepatic lobe, correctly classified 39 of 46 SPECT/biopsy pairs.

"In conclusion, this pilot trial identified SPECT parameters that correlated with liver histology changes," the researchers wrote, although "a larger study is needed to demonstrate whether SPECT parameters alone or with other markers can provide information on fibrosis with the clinical significance obtained through liver biopsy."

Shiramizu and coauthors published their study in the *Journal of Acquired Immune Deficiency Syndromes* (Correlation of single photon emission computed tomography parameters as a noninvasive alternative to liver biopsies in assessing liver involvement in the setting of HIV and hepatitis C virus coinfection: A multicenter trial of the adult AIDS clinical. *JAIDS*, 2003;33(3):329-335).

Source: *Hepatitis Weekly*

New Technology Uses Yeast to Produce Proteins; Process Could Create Drugs for Hemophilia and Other Therapies

August 29, 2003

Scientists working in the US recently said they had figured out how to use yeast to make vital human proteins. The scientists hope the technology can be

put to work producing human proteins in large quantities and make it possible to use as drug proteins that now cannot be mass-produced, including factors to treat hemophilia, along with proteins used to boost the blood cells of cancer patients, multiple sclerosis drugs and others.

Some human proteins, such as insulin, can be made cheaply now using bacteria. The bacteria are simply genetically engineered to make the protein. However, this process only works with some proteins. Many, including factor, have to be made using batches of cells from mammals. This process is expensive, difficult to maintain and potentially carries the threat of transferring animal retroviruses to the human protein. In addition, these processes take considerable time to produce a protein, where yeast takes three to four days, sources said.

Source: *Sun-Sentinel* (Fort Lauderdale, Florida)

Previous HCV treatment reduces risk of liver toxicity during HIV treatment

August 27, 2003

Previous treatment for hepatitis C reduces the risk of liver toxicity during HIV treatment in coinfected patients, according to researcher C. Uberti-Foppa and colleagues at Vita-Salute San Rafaele University in Milan. The researchers compared "the incidence of progression to severe antiretroviral-related liver toxicity in 66 patients pretreated (36 with interferon-alpha IFNalpha , 30 with IFNalpha plus ribavirin), and 39 patients not pretreated."

"The subjects could choose whether to receive anti-HCV therapy," they noted in the Journal of Acquired Immune Deficiency Syndromes. "Severe liver toxicity was defined as alanine aminotransferase (ALT) level greater than or equal to five times the upper limit of normal in patients with normal baseline levels and greater than or equal to 3.5-times in those with increased baseline levels." The investigators "also estimated the hepatotoxicity-related risk of discontinuing antiretroviral therapy." Their results "suggest that previous treatment of chronic active HCV is an independent factor associated with a decrease of severe liver toxicity as the result of a subsequent antiretroviral regimen." In addition, their findings "confirm that the baseline level of ALT is an important prognostic factor for increased liver damage during antiretroviral therapy."

Source: *Biotech Weekly*

Early response to individualized weight-based PegIntron and Rebetol hepatitis C therapy allows accurate prediction of treatment success

August 27, 2003

Early virologic response (EVR) in patients with chronic hepatitis C following 12 weeks of individualized, weight-based dosing of PegIntron and Rebetol (ribavirin) combination therapy can accurately predict the likely outcome of a full, 48-week course of treatment, according to a paper appearing in the current issue of *Hepatology*. The findings show that EVR is important to physicians in making treatment decisions and to patients as a treatment milestone. This analysis is consistent with the current European Union (EU) labeling for PegIntron.

As noted in the paper, 76 per cent of patients demonstrated an EVR following 12 weeks of individualized, weight-based dosing of PegIntron and Rebetol combination therapy, and, of those, 80 per cent of patients went on to achieve a sustained virologic response (SVR) after full treatment. EVR is defined as at least a 99 per cent (2 log10)

reduction in hepatitis C virus (HCV) load at week 12 of therapy. SVR is defined as the sustained undetectability of HCV six months following 48 weeks of treatment and is the accepted criterion for efficacy.

PegIntron and Rebetol combination therapy is the most prescribed treatment for HCV worldwide and is indicated for the treatment of chronic HCV in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age. More than 300,000 HCV patients worldwide, including 150,000 US patients, have received this combination therapy since its introduction in 2001.

Source: PR Newswire Europe

BLOOD SAFETY NEWS

West Nile Virus Update

Detection of West Nile Virus in Blood Donations

September 3, 2003

During the 2002 epidemic of West Nile virus (WNV) in the United States, a total of 23 persons were reported to have acquired WNV infection after receipt of blood components from 16 WNV-viremic blood donors[1], and an estimated 500 viremic donations might have been collected (B. Biggerstaff, MD, Centers for Disease Control, personal communication, 2003). Because of the possibility of recurrent WNV epidemics in the United States, blood collection agencies (BCAs) recently implemented WNV nucleic acid--amplification tests (NATs) to screen all donations and quarantine and retrieve potentially infectious blood components. In addition to NAT screening, the Food and Drug Administration (FDA) recommended that BCAs enhance donor deferral questions by specifically asking about fever with headache occurring in the week before donation and defer persons reporting such symptoms[2]. This report describes the NAT screening process for two WNV-viremic donors and presents data summarizing the testing results for approximately 95% of the civilian blood donations collected during late June to early August. These preliminary data suggest that investigational screening tests are effective in identifying viremic donations and preventing the implicated blood components from entering the blood supply.

Screening Procedures

Two commercial WNV-screening NATs have been distributed under phase III investigational new drug (IND) approval by FDA. The Roche assay is based on a real-time, quantitative reverse transcriptase polymerase chain reaction (PCR) format (Taqman®), and the GenProbe-Chiron assay is based on a transcription-mediated amplification format. Both assays identify highly conserved regions of the WNV genome. Depending on the test format, aliquots of the donation are combined with aliquots from other donors into pools of six (Roche assay) or 16 (GenProbe-Chiron assay) for NAT. If the pool is NAT-reactive, the individual samples that had been combined are tested separately by using the same NAT-screening format. Some laboratories test individual donations with no pooling. When an individual donation is NAT-reactive, all blood components associated with that donation are quarantined; unused components from any donation given by the same donor within the preceding 14 to 28 days are retrieved. As part of the test evaluation under the investigational status, a series of additional NATs are performed on alternate samples from the implicated donation (ie, an aliquot from the donated plasma).

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Additional amplification testing is usually performed by a second laboratory using a different amplification format or primers that are reactive with a different part of the WNV genome. The original donation sample and blood samples collected after the donation are assayed for WNV-specific IgM antibody to document seroconversion in the donor. Donor information, including recent travel history, other exposure history and review of symptoms compatible with WNV illness before or after donation, is collected by questionnaire within 14 days of donation.

To assist with national WNV surveillance and control efforts, BCAs share WNV NAT-screening data with state health departments. Full confirmatory testing under the IND protocols might not be completed in time to serve public health needs; therefore, preliminary screening results are reported to the state health department of the donor's state of residence. Donors are presumed to be WNV viremic when samples from the initial donation are reactive in the screening NATs of the pool, reactive using the screening NAT as individual samples and repeatedly reactive as individual samples using an additional NAT. The American Association of Blood Banks, CDC and FDA collaborated to request BCAs to report the state of residence, age, sex, postal code, and date of donation of presumptive viremic donors[3].

Examples of NAT Screening Process

Donor 1. On June 25, 2003, a resident of Harris County, Texas, aged 47 years donated blood locally. A pool of six samples, including this donation, was reactive on NAT screening performed the same day. When individual donations were tested, this person's donation was the only reactive donation identified from the initially reactive pool. A sample of the plasma component (ie, alternate sample) was tested on June 26 by using the same NAT format and was found to be reactive. On June 27 the BCA reported this case to the Harris County Public Health and Environmental Services as a presumptive WNV infection. Subsequent PCR testing using alternate primers and NAT formats at three different laboratories, including CDC, confirmed the presence of WNV RNA in the blood with an estimated viral load of 7,200 copies/mL (18 plaque-forming units [pfu]/mL). Plasma samples collected from this donor by the BCA 14 and 28 days post-donation did not contain WNV RNA; serologic testing is pending. The donor reported no symptoms suggestive of WNV illness either before donation or during the four weeks post-donation. On July 2 the NAT manufacturer reported having sequenced an amplicon (ie, the amplified segment of viral genome generated by PCR) that was homologous with the 1999 New York strain of WNV. At CDC, WNV was isolated from the plasma. This donor would be eligible to donate blood again 28 days after the original donation (ie, the most recent reactive NAT result) according to the IND protocol.

Donor 2. On July 9 a South Dakota resident aged 24 years donated blood locally. On July 10 initial screening of the pool of six samples was NAT-reactive. Testing of the individual donor's sample also was reactive on this date, and the BCA notified the South Dakota Department of Health. Aliquots of the donated plasma were tested by using alternate WNV primers and NAT formats at a second laboratory, the South Dakota Public Department of Health State Laboratory and CDC; all tests were reactive. The viral load was estimated to be 160,000 copies/mL (400 pfu/mL). WNV-specific antibody was identified in a sample collected 14 days post-donation; the donor reported fever and malaise from the second day to the fourth day post-donation.

Status of Blood Donation Screening for WNV

Of the approximately one million donations screened as of August 5, a total of 329 (approximately 0.03%) were found reactive for WNV infec-

tion by using the NAT format. Of these 329 donations, 163 (approximately 0.015% of total donations) were repeatedly reactive when tested with an additional NAT; results of additional NATs for 28 screening test--reactive donations are pending. The more than one million donations screened represent approximately 95% of the blood collected in the US during that period; however, testing was performed on all donations. As of August 5 state health departments have reported 38 presumptive WNV-viremic donors to ArboNET, the cooperative surveillance project between CDC and 57 state and local health departments. These presumptive WNV-viremic donors have been reported from Colorado, Florida, Louisiana, Mississippi, New Mexico, South Dakota and Texas. The remaining donors identified by the BCA community have yet to be reported to public health officials in the donors' states of residence or have not yet been reported to ArboNET by public health departments.

Reported by: SL Stramer, PhD, American Red Cross, Gaithersburg, Maryland. S Caglioti, Blood Systems Laboratories, Tempe, Arizona. DM Strong, PhD, Puget Sound Blood Center, Seattle, Washington. K Sazama, MD, Anderson Cancer Center, Houston, Texas. W Dickey, MD, Bonfils Blood Center, Denver, Colorado. S Kleinman, MD, American Association of Blood Banks, Victoria, British Columbia, Canada. H Nakhasi, J Epstein, J Goodman, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. MJ Kuehnert, MD, Div of Viral and Rickettsial Diseases; A Marfin, MD, N Crall, Div of Vector-Borne Infectious Diseases, National Center for Infectious Diseases; S Montgomery, DVM, EIS Officer, CDC.

Editorial Note:
On the basis of information gathered from BCAs, the investigational screening tests currently in use are successfully identifying viremic donations and preventing the implicated blood components from entering the blood supply. Follow-up testing and data collection performed by BCAs on all presumptive viremic donors identified by the initial screening tests are necessary to confirm these infections, but identification of probable infections might be valuable to surveillance efforts at the state level.

The WNV-screening NAT was commercially developed and implemented during a nine-month period, from September 2002, when the need was identified, to the initiation of donation testing in June 2003. As of July 14 all civilian blood donations collected in the United States, including Puerto Rico, have been screened for WNV by using NATs. WNV nucleic-acid detection was identified as the most efficient means of interdicting viremic donations, as opposed to donor deferral on the basis of donor symptoms or serologic testing. In addition, since 1999 all blood donations have been screened for human immunodeficiency virus-1 and hepatitis C virus by virus detection using NAT-based methods in a pooled screening format. As a result, testing infrastructure and familiarity with these methods and formats were in place at regional blood screening laboratories. Although the technology for NAT of sample pools will probably detect the majority of viremic donations, the sensitivity of testing in field settings is still under investigation. As a result, patients who have received blood transfusions within four weeks preceding the development of febrile illness compatible with WNV infection should be reported to CDC through the local public health authorities to initiate an investigation.

WNV viremia in humans typically lasts an average of six days[4,5] and is thought to peak shortly before or within a few days of the onset of symptoms among persons who have WNV illness[6]. After illness onset, the concentration of virus in the bloodstream decreases, and detectable amounts of WNV-specific IgM antibody increase. During the investigations of clinical illness resulting from transfusion of

WNV-infectious blood products in 2002, the implicated donors were estimated to have had viremia as low as 0.8 pfu/mL, and many were asymptomatic in the week before or after donation. In all cases in which transfusion transmission of WNV infection was proven, the donated blood was negative for IgM. However, the possibility of transfusion transmission from donors with detectable IgM concurrent with low-level viremia has not been excluded.

After the issuance of industry-wide guidelines from the American Association of Blood Banks [3], which allow for protection of blood donor confidentiality, reporting to public health officials of presumed positive donors has been performed voluntarily by blood banks in several states. The current investigational screening tests are designed to be sensitive for the initial testing of pooled samples from as many as 16 donors. Because of the high sensitivity of these tests, public health officials should be cautious in the use of preliminary test result data because false-positive results can occur. As part of the protocols for evaluation of these investigational tests, all blood products from a donation found to be WNV-reactive on initial individual donation screening are excluded from the blood supply. Because the majority of WNV-infected persons remain asymptomatic, collection of data about viremic donors might serve as an essential surveillance tool in addition to screening for removal of potentially infectious products from the blood supply. State health departments receiving reports of these donors are encouraged to notify CDC through ArboNET as part of the national surveillance of human WNV infection.

Acknowledgments:
This report is based on contributions by S Rossmann, MD, Gulf Coast Regional Blood Bank, Houston, Texas. L Kightlinger, PhD, South Dakota Dept of Public Health. R Dodd, PhD, American Red Cross, Rockville, Maryland. BG Bartley, MSc, Armed Svcs Blood Program Office, Falls Church, Virginia. RS Lanciotti, PhD, JT Roehrig, PhD, GL Campbell, MD, LR Petersen, MD, Div of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, CDC.

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Source: *CDC Morbidity and Mortality Weekly Report*

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Health and Human Services Responds to the Advisory Committee on Blood Safety and Availability and Bleeding Disorders Community

September 1, 2003

The Department of Health and Human Services (HHS) has formally responded to concerns arising from its April 28, 2003, letter questioning the cost-effectiveness of recombinant clotting factor products. The letter, from Acting Assistant Secretary of Health Richard Carmona, MD was provided to HHS's Advisory Committee on Blood Safety and Availability (BSA) at its May meeting in response to BSA recommending revisions to the Medicare carrier instruction manual. BSA had recommended updating the manual to better reflect current standards of care for bleeding disorders.

BSA Committee members and the bleeding disorders community were very concerned with the HHS response and its suggestion of cost-effectiveness analysis, which did not include adequate consideration of safety. BSA Chair Mark Brecher, MD, met with Department officials in July to convey the committee's and community's concerns. In its July 21, 2003, response letter, HHS clarifies, "There was never the intent on the part of the Department...to discourage the use of recombinant clotting factor." The letter adds, "The Department is acutely aware of the concerns of the hemophilia community had no desire to imply in any way that the Department was not concerned about their safety."

In addition to its response to the Committee, the Department also individually responded to two organizations represented on BSA. These letters, which have been provided to NHF, further state, " We have no desire to limit the therapeutic options available to the bleeding disorders community."

The Department is further preparing a separate communication forwarding the Committee's original recommendation to the Centers for Medicare and Medicaid Services, encouraging the updating of the carrier manual language. BSA first considered this action outdated language, which referred to heat and non-heat treated product, might inappropriately be used by state and private payers to limit access to recombinant clotting factor products.

NHF NEWS

Gina S. Shreve, PhD, Steps Down as NHF as NHF President

August 29, 2003

Gina S. Shreve, PhD, has announced her decision to step down from her position as National Hemophilia Foundation President for personal and professional reasons. Dr. Shreve has held the position since November of 2002. She will continue to serve on the NHF board as an active volunteer. Jordan Lurie, MD, the president-elect and a member of the board, will serve as the acting president effective immediately.

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Project Red Flag on Fox News

September 7, 2003

On Sunday, September 7th, the New York-based news show ***Fox and Friends*** will include a live interview with Dr. Paula Elbirt, co-chair of the NHF Project Red Flag Women's Task Force. She will discuss the urgent need to raise awareness across the country about the fact that women can and do have bleeding disorders. She will also present the results of a new survey that clearly demonstrate that women are unaware that a bleeding disorder may be the cause of excessive menstrual bleeding. NHF will provide an update on the availability of videotape copies of the segment after show.

Many Stories, One Voice

NHF's 55th Annual Meeting Update

Meeting fever has set in at the New York office as registrations flow in. In the beautiful setting of Salt Lake City, Utah, the annual meeting working group 2003 has developed a top-notch program of education and events.

- Take the ***Do the 5!*** prevention quiz at exhibit booths during the opening reception and be part of a raffle for free round-trip tickets to the 56th Annual Meeting.
- As a parent, grandparent or guardian, learn skills and coping strategies in a strong array of sessions, including:
  - Bleeding Disorders 101—Ask the Experts
  - Parenting Skills—How Children Understand Hemophilia
  - New Options for Prophylaxis
  - Inhibitors, Ports and Prophylaxis
  - National Prevention Program Report Out

The full program schedule-with tracks for healthcare providers, our chapter staff organization (CSO) and consumers of all ages, as well as our Youth and Adolescent Program featuring zoo and planetarium field trips-is just a click away. For more information log onto our Web site, www.hemophilia.org, or call 800 424-2634, ext. 4.

NHF and Aventis Behring Sponsor Junior National Championship

NHF and Aventis Behring are cosponsoring the Junior National Championship, free, fun-filled days of physical activity and friendly competition for youth. One successful event has already taken place on August 23rd in Portland, Oregon. Upcoming events will be held in Minneapolis, Minnesota, Dallas, Texas, and Tampa, Florida. The events will be hosted by Perry Parker, a professional golfer with hemophilia, and Cory Parker, a professional baseball player with hemophilia. For more information including dates, or to register, log on to www.hemophilia.org