

# THE HEMOPHILIA BULLETIN

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**World Federation of Hemophilia Meetings**, in September, 2005

## Musculoskeletal Committee

Orthopedic surgeons, physiatrists, physiotherapists and others met in historic, bustling, hospitable Istanbul. It's modern. It's exotic.

Dealing with **chronic synovitis** remains a major issue around the world. Onder Kilicoglu of Istanbul and Semih Aydogdu of Izmir both reported gratifying responses to **radionucleotide synovectomy**, if joint damage was not advanced. Shubhranshu Mohanty, of Mumbai, India, got special government permission to try **rifampicin**, pioneered for synovitis by Federico Fernandez-Palazzi of Venezuela. After a modest dose of concentrate, Dr. Mohanty aspirated the joint, injected 150-300 mg rifampicin in 2-5 ml saline, applied cold packs for 20 minutes and compression for 24 hours. Physiotherapy was given for the next six days. The sequence was repeated weekly for six weeks. He treated 13 joints (including 9 knees) in 11 patients. Results were excellent results (no hemarthrosis or chronic pain) in 9 patients, good results (no hemarthrosis but pain) in three, and poor in one whose shoulder joint was treated. Although radioisotopes give fast relief, they are troublesome to use because of their expense and short half-lives. There also is concern about the two cases of leukemia that developed in children in the USA who had had radioisotope synovectomies. The procedure has been used for decades for rheumatoid arthritis as well as for other forms of synovitis. We do not yet have sufficient follow-up data to comment usefully on these two events.

**Surgery in the presence of inhibitors** was described. Ivan Hvid of Denmark reviewed his experience in careful detail. He uses NovoSeven, 75-125 mg/kg pre-op then every two hours for 10-30 doses, plus tranexamic acid. He does use electrocautery but does not use local hemostatic agents. He said, however, that a case could be made for using fibrin sealants. He managed four patients with high inhibitor levels, for a total of 12 operations (counting a bilateral total knee replacement as two operations). Four operations were complicated, two by bleeding or hematoma requiring re-operation, one (a knee) by arthrofibrosis and one by formation of a pseudotumor. The latter was secondary to a large hematoma forming after open reduction, internal fixation at the hip; it was treated with excision. In five total knee replacements, the mean intra-operative blood loss was 500 ml and the mean post-op blood loss was 770 ml. Marvin Gilbert of New York encourages surgeons to report any more inhibitor patients undergoing orthopedic surgery to the Committee's registry, which now lists 52 such operations.

Carlos Rodriguez-Merchan of Madrid described a patient who appeared to have a pseudotumor of the tibia that turned out to be a highly-malignant non-Hodgkins lymphoma. Nicholas Goddard of London said that he, too, had seen a "**pseudo-pseudotumor**" that turned out to be a sarcoma.

Kathy Mulder of Winnipeg described the changes in muscle length and strength, position sense and posture that may result when a patient has a target joint or chronic synovitis. Optimal rehabilitation consists not only of muscle strengthening but also of specific exercises to promote **proprioception and balance**.

Lily Heijnen of Utrecht gave an impassioned plea for **more physiotherapy** (PT) for persons with hemophilia, and for extension of that therapy outside major hospitals into the community. She emphasized that physiotherapists need to be **paid team members**, not just volunteers. I had no idea that they were being recruited as volunteers. I've seen surgeons, including oral surgeons, donate time to hemophilia; their involvement may be somewhat sporadic. Lower-paid health-care workers cannot afford to donate a lot of time. Dr. Heijnen struck a note with me, for I was impressed with how much benefit could be conferred with a course of PT back in the days when all we had was plasma. Some patients with inhibitors were treated gently and gradually without plasma. Muscles may lose strength rapidly upon inactivity but they can gain strength rapidly, too. I am wary of "prophylaxis" that consists of concentrate alone. I was introduced to prophylaxis by observing Hans Brackmann's clinic in Bonn in 1981. He gave modest doses of concentrate three times weekly to children with severe hemophilia A. With equal enthusiasm, he taught simple exercises. He measured quadriceps strength in every patient. He congratulated those who had improved since the previous visit, and exhorted those who had regressed. I suspect that prophylactic PT would potentiate concentrate prophylaxis (preventing hemorrhages and saving money). Why is this cost-effective and relatively inexpensive therapy not more popular? Why don't patients and hemophilia societies demand more PT? To the patient, perhaps, it sounds like hard work. Maybe it ought to be promoted as cosmetic: "Be buff! Be a muscle-man!" But if it sounds like fun, insurance companies may look askance at it. How do we start prophylaxis with babies? My own babies splashed vigorously in a pool before they could walk. Pools don't have to be fancy.

I liked Kaan Kavakli's report from Izmir on the rehabilitation of **ileopsoas hemorrhages**. In my experience, rehabilitation takes a long time and recurrence is common. Dr. Kavakli has ultrasound evidence that a hematoma can take as long as three months to resorb. Our doctrine always was, mobilize slowly, resume activity cautiously. Diagnosis and management of bleeding into this well-hidden muscle separates the experienced from the naive doctor.

The **Henry Horoszowski award**, for best paper presented, went to **Frank van Genderen** of Utrecht who developed and validated a hemophilia-specific self-assessment questionnaire on functional abilities. Standardized assessment tools are vital for following progress in treatment methods. Tools specific for hemophilia, such as the Petterson score, are more useful than non-specific ones.

A **new award** was announced, named for the late Vincenzo Pietrogrande of Milan, who helped found the Musculoskeletal Committee. It recognizes the lifetime achievement of a professional dedicated to the musculoskeletal care of persons with hemophilia who also has supported the extension of knowledge to other professionals, as through the Musculoskeletal Committee. The first recipient was **Marvin Gilbert**.

## Global Forum

Montreal was the venue for WFH's conclave on the safety and availability of concentrates world-wide. Some topics previously covered in these pages are not reported here in detail.

Mark Skinner promoted identification of more of the potential recipients of therapy, that is, persons with bleeding disorders, through **registries**. Documentation of the number of patients helps enlist the interest of pharmaceutical companies and of governments.

Despite the high cost of concentrate, objective **studies of dosage** are rare. Alok Srivastava of Vellore, India, found 13 small studies, all performed more than 20 years ago, describing lower doses than are now in common use. Analysis of thrombin generation assays shows a near normal response at about 30% plasma FVIII levels. Dr. Srivastava reviewed Dutch data on dosage and outcome from the 1970's to 90's. As more patients got onto the home program and onto prophylaxis, and as the weekly dose for prophylaxis doubled over those decades, the number of joint hemorrhages fell (but they were not eliminated) and the average Petterson score declined. Dr. Srivastava argues that whereas increasing the yearly consumption of concentrate does reduce hemorrhages and joint damage, one need not despair if those doses cannot be imitated in poorer countries. An intermediate level of factor replacement, 1000-2000 units/kg/year, may serve to preserve functional independence. (That dosage level is the current target in Brazil.) For surgical operations in Vellore, Dr. Srivastava uses a pre-operative dose that raises the plasma FVIII level to 80-100% and post-operative doses maintaining a trough level of 20-40%. His dosage scheme is similar to mine with early (1968-1970's) elective orthopedic surgeries in Los Angeles at Orthopaedic Hospital. I agree that dosage has escalated in the western world without evidence that higher doses are necessary or advantageous. I suspect that very good results could be obtained with more modest doses. We should make optimal use of less-expensive agents: physiotherapy as prophylaxis, DDAVP where appropriate, local hemostatic agents in surgery and tooth extraction, anti-fibrinolytic agents in tooth extraction. Good management with lesser doses of concentrate requires careful attention from someone devoted and expert. That may be the problem. Where the cost of concentrate is not an issue, it's easy to just give higher doses and ignore the alternatives.

**Why does Dr. Srivastava fuss about dosage**, why doesn't he just go ahead and use lower doses for his underprivileged patients, as he has been doing so successfully? Patients everywhere want to know that they are being treated well. They ask, why do I get such a low dose when a patient in, say, Los Angeles, gets more? A man in Vellore might feel discriminated against, when, in reality, he is being managed much more scientifically than a man in Los Angeles.

Pier Mannucci of Milan points out that the **consumption of FVIII increased** from 1990 to 2000 **in the developing world**, for example, from 48 million IU/year to 328 IU/year in South America, from 152 IU/year to 225 IU/year in Asia. Production of plasma-derived FVIII

increased from 1.3 to 2.1 billion IU/year over the past 18 years. Recombinant FVIII added to the total supply, accounting for 48% of all FVIII used in the world and 88% of that used in Europe and North America. (Albert Farrugia said that the top five plasma fractionators account for 58% of global sales.)

Dr. Mannucci will spearhead a **study** in eastern Europe and the Middle East **on the incidence of inhibitors in patients on plasma-derived versus recombinant FVIII**, an issue not settled. Several studies suggest that use of a single plasma-derived concentrate is associated with a lower rate of inhibitor formation in previously-untreated patients (less than 10%) than is associated with use of multiple plasma-derived concentrates (about 20%) or recombinant concentrates. All single-product surveys were of a product made and used within the same country, e.g. French concentrate for French patients, Italian concentrate for Italian patients, and so on.

Dr. Mannucci also reviewed the evidence for **safety of concentrates from pathogens**. There has been no transmission of known pathogens with current concentrates, whether plasma-derived or recombinant. Albert Farrugia of Australia stated firmly that recombinants are biologicals, not synthetic drugs. Recombinants are made in cultures of hamster cells transfected with human genes for the clotting factor desired. All cell lines, he said, are susceptible to prion infection (but no such instance has been reported). There is a public perception that the risk of pathogen infection is lower if recombinants are used instead of plasma-derived products, but any additional safety margin is small. Is that advantage, if real, worth the disadvantage of more inhibitor provocation, if that, too, is real? (It may be that the risks, if any, of recombinants and of plasma-derived concentrates are equal.)

Widely-different **estimations of the risk of transmission of new variant Creutzfeld-Jacob disease by concentrates made in the UK from UK plasma** have been issued by the UK and by the FDA. Two persons in the UK had vCJD that may have been acquired from whole blood transfusion. David Page quoted the UK risk assessment: "It is likely that many patients with bleeding disorders will have been exposed to a potential additional risk of 1% or greater". Patients with hemophilia are being notified of that risk and have been told to inform their doctors and dentists. Surgical and dental instruments are to be disposable, but no additional funding has been provided. Patients have been stigmatized, and turned away from dentists and hospitals. (Strangely, persons with hemophilia have been singled out for notification of their supposed increased risk while recipients of cellular blood products are not being notified.) At the FDA, and in Canada (which used some specialized products such as factor XI, from the UK), the same data on vCJD, the same experiments, were evaluated, and the risk assessed as very low. The UK seems to have made their calculations using worst-case scenarios and discounting hopeful data. The USA is involved only insofar as about 50 patients with factor XI deficiency were treated with British factor XI concentrate. Mark Weinstein of the FDA reviewed the assumptions on which FDA risk estimates were based. I was not able to copy them all down as he rapidly spoke. He said they would be posted on the FDA website ([www.fda.gov](http://www.fda.gov)) but they were not yet there as I wrote this. Major considerations include the (minimal) evidence of prevalence of unsymptomatic vCJD infection in the UK, level of abnormal prions in plasma of affected persons, infectivity of plasma, the amount of prions needed for an infectious dose, and the reduction of any contamination by plasma fractionation and viral inactivation. **The FDA will recommend that patients who received factor XI concentrate made from UK plasma be notified that some risk may**

**exist.** They will be asked not to donate blood or organs. They will be encouraged to stay in touch with their hemophilia center. Patients themselves will decide whether to notify surgeons and dentists and will be told that such notification may negatively impact their access to health care. They will be told where to find detailed information on the Internet.

It has long been the dream of David Page of Canada to get that country's excess cryoprecipitate paste (bulk cryoprecipitate) turned into concentrate for the use of the developing world. Duncan Armstrong of the National Bioproducts Institute (NBI), in Durban, South Africa, is willing to **turn Canadian cryoprecipitate paste into concentrate for the use of needy patients in southern Africa.** NBI traditionally has supported the concentrate needs of neighboring countries. They may be able to expand the effort thanks to this initiative, which has required the collaboration of WHO, WFH, the major Canadian blood procurement agencies, NBI, and the South African Hemophilia Foundation.

Graham Sher of the Canadian Blood Services (CBS) described some of their economics. (The province of Quebec has a separate but co-operating system called Hema-Quebec.) CBS pays for all plasma protein products, plasma-derived or recombinant. In 2004-5, half of their budget went to plasma products, and 42% of that budget was spent on recombinants. CBS and Hema-Quebec ship about 190,000 liters of plasma for fractionation into gamma globulin (IVIG) and albumin by Talecris (previously Bayer) in Clayton, North Carolina. They meet about 24% of Canadian needs for IVIG. The remainder comes from commercial sources, made from US plasma. Canada has **changed its philosophy about plasma self-sufficiency.** Formerly, it tried to provide all the plasma needed for fractionation for its own use; now, it hopes to provide 40% of that plasma. In the fiscal year 1993-4, Canada used 56.1 million IU of plasma-derived FVIII and 21.7 million IU of the newly-introduced recombinant FVIII. In 2004, 4.3 million IU of plasma-derived FVIII and 130.2 million IU of recombinant FVIII were used in Canada (a 73% increase in FVIII use.) Major current uses for plasma-derived FVIII include von Willebrand disease and induction of immune tolerance. In 1993, the amount of plasma shipped for fractionation was 239,000 liters (64% recovered from whole blood, 24% from apheresis). By 2004, the amount of plasma shipped for fractionation had dropped to 192,000 liters, thanks to virtual disappearance of apheresis plasma with abandonment of plasma self-sufficiency.

Thierry Burnouf addressed the question, **is potentially-useful plasma being wasted?** Internationally, some 25-30 million liters of plasma is fractionated; including recovered and apheresis plasma. The theoretical yield of FVIII from that plasma could be as much as 4.3 billion units, but even if all that were turned into concentrate, it would not meet the needs of all persons in the world with hemophilia. Theoretically, some 16 million liters of plasma is recovered from the 80 million whole blood collections world-wide. Of that, some 3 million liters are used as whole plasma transfusions. Of the remaining 13 million liters, less than half goes into fractionation. The un-fractionated half may be made into pastes: cryoprecipitate, Fraction IV (for alpha-1-antitrypsin), Fraction V (albumin) and Fractions II-III (gamma globulin). Quality issues may limit the usefulness of cryoprecipitate paste. The plasma may not have been separated promptly from red blood cells, or frozen or stored at optimal temperatures, affecting potency. When potency is lost, then the cost of all the processing (donor testing, etc.) may be excessive in relation to the value of the final products. Around the world, very few places have high-quality excess plasma. Most of the unused plasma in the world comes from lower-quality sources (e.g. where few donor tests are

done.) At the moment, only Canada appears to be a source of good-quality unused cryoprecipitate paste. Use of Australian cryoprecipitate paste might be considered. They are transferring to recombinant FVIII. Their laws, however, currently forbid export of blood products.

Albert Farrugia detailed the **effect of plasma collection measures, under control of a blood or plasma bank, on retention of FVIII,** as follows. (1) The anticoagulant has an effect. E.g., if apheresis is performed with low-level citrate anticoagulant, the recovery of FVIII is 13% better than with regular citrate. (2) The collection method matters. The recovery of FVIII in apheresis plasma is 12% better than in plasma recovered from whole blood donation. (Plasma is processed much faster with apheresis). If apheresis is performed with continuous-flow machines (e.g. Haemonetics), 18% more cryoprecipitate is extracted than with manual, one-bag-at-a-time apheresis. (3) The interval between blood collection and its centrifugation and freezing of the plasma is crucial. The greater the delay, the more FVIII is lost. If plasma is frozen within 4 hours of blood collection, it contains 11% more FVIII than if it is frozen at 6-8 hours after collection (routine for FVIII preservation), and 20.5% more FVIII than if it is frozen at 16-18 hours after collection, as is commonplace. (4) The freezing rate may be important. A small amount of evidence suggests that rapid freezing with equipment that allows the plasma to reach -30° C in 30 minutes preserves FVIII better than slower freezing, with attainment of that low temperature in 3-4 hours. (5) The storage conditions of frozen plasma definitely matter. Plasma can be held many months at -30° C, or even at -20° C, the latter if there is no intermittent warming to a higher temperature. It's more important to have a steady temperature than a particular low temperature. Thawing and refreezing is detrimental to FVIII yield. These precautions also are important for production of good quality albumin and gamma globulin. "Factor VIII is an exquisite marker for the overall quality of the plasma", said Dr. Farrugia.

Is blood-bank manufactured **cryoprecipitate** a lost cause? It's made and used widely in the developing world. I have reported previously on its remarkable success in Thailand, where a combination of carefully-chosen repeat donors and a viral inactivation step have kept it safe. Thai blood bankers also studied the production of good quality blood bags and transferred the technique to their own country to reduce a major cost. Gail Rock of Canada reminded us, as did Albert Farrugia, that preservation of FVIII in cryo is a matter of attention to each step in the production process. She recalled her studies, a quarter of a century ago, on **improving FVIII stability** in plasma, and FVIII yield in cryo made from it, by using **heparin as the anticoagulant** instead of citrate. At the time, as now, there was hesitation to consider a different anticoagulant. Heparin can be added to citrated plasma to confer some of its stabilizing effect. It's possible to heat-treat cryo to 80°C for excellent viral-inactivation. Or, whole plasma can be sterilized with a variety of agents, such as solvent-detergent, methylene blue, psoralens, or riboflavin, and cryoprecipitate made from treated plasma. Some of these procedures could be adapted to a blood bank. Cryo's dismissal by WFH as an acceptable therapy was based on the estimated viral-transmission risk with non-viral-inactivated cryo from random donors, a bad-case scenario.

Trevor Barrowcliffe of the UK's National Institute for Biological Standards and Controls described a **controversy about concentrate labeling.** Should potency be "nominal", that is, standard sizes of 250, 500, 1000 IU per vial, which represent approximations; nominal labeling is used in most of Europe. Or, should it be "actual", the result of the manufacturer's assay, such as 475 IU, 1013 IU, etc, as is used in the

USA. Or, should it be dual ("500 IU, content 475" etc.) as is the practice in the UK. Dr. Barrowcliffe likes the dual method. I like either the actual or the dual method. With the actual assay, we can avoid overdosing and underdosing. Use of actual assays would discourage habitual underfilling, quite possible with the nominal method, given that the regulator allows for substantial error of the assays.

Donna DiMichele of New York and Paula Bolton-Maggs of Manchester, UK, both reviewed the **rare bleeding disorders** and the limited products available to treat them. Dr. Bolton-Maggs noted that certain prothrombin complexes contain three factors, prothrombin, factor IX and factor X (DEFIX HT from Scotland, and Prothromplex from Baxter in Vienna) and two others contain those factors plus a fourth, factor VII (Beriplex made in Germany by ZLB Behring and Prothromplex T from Baxter-Vienna). Some clinicians are worried about the presence of factor VII, its level of activation and a thrombogenicity risk. For factor VII deficiency, a plasma-derived factor VII concentrate is made by Baxter in Vienna and is available in Europe (and Canada) but not in the USA. The British factor VII concentrate has been discontinued, the French factor VII is being discontinued. (Dr. Falcou of LFB in France confirmed that news. He said that there were two major reasons: NovoSeven is licensed for the indication of factor VII deficiency and is providing strong competition, and, the French factor VII has only a single viral inactivation step. Adding a second, as is the modern expectation of regulators, would require new clinical trials.) Products for treatment of factor X deficiency include the prothrombin complexes used for prothrombin deficiency plus Kaskadil from LFB (containing X and VII) and Grifols' Profilnine. There still are factor XI concentrates, one made in the UK (from US plasma) by BPL and one in France by LFB. (The latter is already double-viral-inactivated and will not be withdrawn.)

**Bulk purchase of concentrate**, as for a given country, can be complex. It's important to get a suitable concentrate, without actual or suspected corrupt practices, at a good price, but there are many pitfalls. **WFH soon will put out a publication with suggested guidelines for tender processes.** Brian O'Mahony reported on model processes to consider tenders (bids) for supplies of concentrate on a large-scale basis. He advocates having a scientific advisory committee, including the foremost treaters, to define the types of concentrate required. Selection criteria include safety and efficacy as well as price: a combination known by the jargon "most economically advantageous". "Transparency" is advocated to avoid any suggestion of favoritism or corruption. In Ireland, a video camera records the deliberations of the committee. Suely Meireles Rezende of Belo Horizonte, Brazil, described the process that has emerged, from years of effort, in that country. They, too, describe the attributes of the concentrates they need, and allow companies to bid, taking the lowest price. The bidding is held in an auction open to the public and broadcast live on the Internet. When this program became fully operational, in 2003, they were able to cut the cost of concentrate in half. (That success depended on the existence of a surplus of excellent FVIII at the time. I was amused to learn that the winning bid in Brazil was for the same concentrate that most of our adult patients use. Many of our adults are price-sensitive, have always used plasma-derived products and continue to do so.) Many people commented that it was wise to have multiple suppliers. If a single supplier is chosen, the other bidders may lose interest in the country and not even maintain product licenses.

Mark Brooker, WFH Public Policy Officer, described WFH's **survey of concentrate prices** around the world, part of its general data collection. In 2004, the total consumption of FVIII reported by 49 of the countries

with data was 1.57 billion IU and the total consumption of FIX was 237 million units. He reported the range of prices paid for various FVIII and factor IX concentrates. Some countries, like Brazil, have bargains. I saw little evidence of price-gouging at the upper end. Some countries are paying more than we do in California, in a few instances, up to twice our price. Ten years ago, however, some countries were paying five times our price. (High prices were generated by middle-men, taking advantage of the ignorance of local buyers.)

Claudia Black, WFH's Program Director, described **the distribution of donated concentrate to needy countries**, starting in 1996 with 2.8 million IU and increasing by 2004 to 54 million IU, an excellent achievement, congratulations to WFH! Packing and shipping services are provided by volunteers of Hemophilia of Georgia, in Atlanta. Donations go to registered hemophilia treatment centers and official national member organizations of WFH. They must request donations. Donations went to 55 countries last year. Requests are screened by Assad Haffar, a physician who is the WFH Humanitarian Aid Coordinator. The recipient HTC or NMO must submit a detailed report to WFH on the utilization of the product. WFH loves to get donations with a long shelf-life but deals with donations having as little as a two-month shelf-life, if the recipient agency can accept it.

Jan Bult of the Plasma Protein Therapeutics Association explained that donations of concentrate from pharmaceutical companies depend on selling enough of the major products, albumin and immune globulin, to afford to produce FVIII in surplus of what could be sold.

The World Health Organization has had a standard policy that donated medicines should be no closer to outdate than one year. Neelam Dhingra, the Co-ordinator of Blood Transfusion Safety of WHO, said that WHO is considering reducing that policy to six months for concentrates.

Johannes Dodt of the Paul-Ehrlich Institute in Germany addressed the frequently-asked question of **re-labeling and re-validating** "outdated" concentrate. Most concentrates "outdate" two years after issue. There's a lot of interest in salvaging short-outdate or recently-outdated concentrate to help meet the need in developing countries. Definitions: "shelf-life" is "the period of time a medicinal product is known to stay within acceptable specifications under defined storage conditions." "Expiry date" (outdate) is the "date when a batch of a medicinal product reaches the end of the shelf-life." Many people in the audience believe that lyophilized concentrates are stable for years if refrigerated, that is, they really have a lot longer shelf-life than is being declared. Most of the official shelf-lives, however, are determined by keeping the product at refrigerator temperature for 18 months and then at 20° C for six months. Dr. Dodt feels that attempts at re-validating and re-labeling is inappropriate for a regulatory agency, and should be performed, if desired, by the recipient country; he knows of no instance in which his Institute has done it. He says, if a batch were to be relabeled, it ought to be marked as such.

**Reprints of the (updated) VWD monograph first issued in 2004 are available; email me your name, mailing address, and number requested.**

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