

# THE HEMOPHILIA BULLETIN

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## World Federation of Hemophilia Congress, Bangkok

The biennial WFH Congress in October was a resounding success with a record attendance. Congratulations to Professor Partraporn Isarankura and her committee as well as to the WFH staff, all of whom worked very hard. It was difficult to choose among the many interesting simultaneous sessions.

Brian O'Mahony, president of WFH, stepped down after ten years of inspired leadership. It was a time of enormous growth. There now are some 107 member countries and many development programs, all undertaken in a thrifty and sensible manner. Welcome and the best of luck to the new president, Mark Skinner, former president of the USA's National Hemophilia Foundation.

## Variant CJD (vCJD) and blood products

James Ironside of Edinburgh reminded us that sporadic Creutzfeldt Jacob Disease (sCJD), a disease with abnormal prions affecting about one person in a million, has been around a long time at the same low incidence and that it has been transmitted among humans almost exclusively via CNS material, especially by dura mater transplants and by injections of growth hormone derived from human pituitary glands.

Mad cow disease (bovine spongiform encephalopathy, BSE), also is associated with abnormal prions, but the strain of prions is different as is the epidemiology. The first affected cow was identified in 1986 in the UK. The bovine epidemic peaked in 1993, when more than 3000 cows per month were being diagnosed. Transmission was oral. Cows were being fed with material that included the rendered carcasses of dead cows, a practice quickly forbidden. Effective enforcement, however, took years. Export of contaminated feed and of cows harboring preclinical infections led to slow spread of BSE outside the UK.

Humans in the UK, and some elsewhere, ate beef contaminated with bovine CNS material. A patient with BSE was identified in 1996 and the human disease was called new variant CJD, or vCJD. To date, a total of 149 cases have been diagnosed in the UK, seven in France and one each in Italy, Ireland, Canada and the USA. The French and Italian patients had not been to the UK; the others had lived in the UK. The

human epidemic appears to be subsiding: three new cases were reported in 2003 and two so far in 2004.

The abnormal prions associated with BSE in cattle are identical to those in humans with vCJD, but differ from the abnormal prions in sporadic CJD and in scrapie (in sheep) and in other transmissible spongiform encephalopathies (TSEs).

The human gene for normal prions has a polymorphism at one site, coding for either of two amino acids, methionine or valine. Persons homozygous for the methionine code are much more vulnerable to sporadic and to vCJD, as follows:

	<b>MM</b>	<b>MV</b>	<b>VV</b>
<b>Normal</b>	37%	51%	12%
<b>Sporadic CJD</b>	71%	15%	14%
<b>Variant CJD</b>	100%	0	0

**Are TSEs transmissible by blood or plasma?** Animal experiments were difficult, but eventually showed that LARGE transfusions from an infected animal, even in the preclinical stage, could transmit the disorder, but that different recipient species have widely-varying levels of susceptibility. Some persons with vCJD were known to have been blood donors in the past, before becoming ill. The recipients of those blood donations have been followed. Two recipients now appear to have acquired vCJD through transfusion of leuco-depleted packed red blood cells (PRBC). One, who died of obvious vCJD at age 69 in 2003, had received one unit of PRBC seven and a half years earlier; his genotype was MM like previous human vCJD cases. The donor died of vCJD three years after donation. The second recipient, an elderly woman, died in 2004 of unrelated causes and, on autopsy, was found to have lesions of vCJD, that is, subclinical manifestations. Her genotype was MV, she was a heterozygote.

Is the incubation time in heterozygotes (or VV homozygotes) longer than in MM homozygotes? Will cases in persons with the MV or VV genotype start to emerge, creating a second, later epidemic in the UK? Or will the disorder remain subclinical in persons of those genotypes?

The most alarming report, to me, was of a search for **vCJD lesions in tonsillectomy and appendectomy tissue** from

random persons in the UK. Such lesions were found in three of 12,675 suitable specimens. That extrapolates to 237 preclinical cases per million people in the UK, or over one per 5000 persons. (Their genotypes were not reported.)

Current information suggests that **plasma is as infectious as whole blood**, but white cells are more infectious than red cells or plasma. Leuco-depletion, standard in the UK for several years, reduces infectivity. Nine persons who later developed clinical vCJD donated blood or plasma, for a total of 23 such donations. Their plasma was pooled with other plasma to make factor concentrates. Many persons with bleeding disorders received plasma products that included these donations. None has yet developed vCJD.

But what about other plasma, from UK donors who have not (yet) developed vCJD? Abnormal prions do exist in plasma, at a very low level, in the preclinical stage of vCJD. We do NOT yet have a blood test to detect them.

So what to do? For many years now, the UK has been importing plasma from the USA to make its plasma products. (That's no relief to a UK patient needing PRBC. UK physicians are trying to reduce the use of PRBC.) Recombinant products now are being used in the UK to the extent possible. Plasma concentrates are made from US plasma for rare disorders.

Paul Giangrande explained that the **UK is now notifying all recipients of products derived from UK plasma** between 1980 to 2001 (from the onset of exposure to contaminated beef to the replacement of UK plasma products with other products, and outdate of any old plasma products) **that they are at risk**, probably a very low risk, of vCJD. They are being given the opportunity to be told whether they received batches of concentrate made from the plasma of donors who later developed clinical vCJD. (The implicated batches included 16 of factor VIII concentrate, eight of factor IX, and 77 of albumin excipient, but no factor XI or XIII.) They are being told not to donate blood, tissues or organs. Their general practitioners and dentists are to be notified. There is concern that dental, endoscopic and surgical instruments may be contaminated and there is no secure way to decontaminate them from the sticky prions. Notification of recipients of whole blood transfusion or PRBC has not yet been ordered, if I understand correctly. Some UK products were exported. I've already been asked to contact our patients who received UK factor XI. (Thank heavens, no "implicated" plasma went into its manufacture, and, the total volume received was quite small, because of factor XI's very long 48- to 72-hour half-life.)

Albert Farrugia reviewed **evidence about removal of prions from plasma during normal processing**. Cryoprecipitation removes one log, other precipitation processes such as the use of polyethylene glycol (PEG) or glycine remove 2-2.3 logs. Chromatography or nanofiltration remove several logs. The

stickiness of prions probably contributes to the efficacy of the latter methods, but chromatography columns and filters must be changed often. Early "spiking" experiments were done with scrapie but there is evidence that BSE (vCJD) behaves the same. Dr. Farrugia concludes that the higher-purity products, processed by chromatography and/or nanofiltration, are safer than those produced with precipitation methods alone. The absolute risk of transmission in plasma products is judged to be very low. Have we been hyper-sensitized by the horrors of the HIV epidemic, are we over-reacting? Dr. Farrugia says, we are "proactively addressing the unknown."

### Surgery in patients with inhibitors

Use of **recombinant VIIa (NovoSeven) has made "previously impossible surgery possible"** said orthopedic surgeon Marvin Gilbert. Surgeons are "getting bolder", a large majority of results are good, but surgeons are unhappy with **occasional poor results**, blamed on inadequate hemostasis.

In the UK, said Paul Giangrande, **the dosage of rVIIa for inhibitor surgery has been increased**. Their current dosage schedule is as follows:

- A bolus of 180 ug/kg immediately prior to surgery
- A bolus of 180 ug/kg immediately after surgery
- A bolus of 180 ug/kg every two hours for a maximum of 10 doses, covering the first 24 hours. If hemostasis is satisfactory, the dose can be reduced to 90 ug/kg.
- A bolus of 90 ug/kg every two hours for the next 24 hours
- A bolus of 90 ug/kg every three hours for each of the next three days
- A bolus of 90 ug/kg every four hours thereafter until discharge
- A bolus of 90 ug/kg before each outpatient physiotherapy session thereafter, e.g. once a week.

That's a tremendous amount of the product, typically costing over US\$ 1 million, but the company has made a stop-loss agreement with UK physicians, that is, if a greater amount of VIIa is needed because of complications, it will be provided at no extra charge. So far, physicians are happier with the hemostasis afforded by these higher doses.

Another approach, if rVIIa alone is inadequate, has been to **use FEIBA and rVIIa together** (for acute hemorrhages primarily, rather than for surgical operations). FEIBA contains prothrombin and factors IX and X. Harold Roberts explained why that might make VIIa a more effective hemostatic agent. VIIa needs not only tissue factor but also factors V and X to convert prothrombin to thrombin. VIIa alone, even in double or triple doses, improves the thrombin generation of hemophilic plasma but does not normalize it. Addition of factor X and VIIa

to hemophilic plasma improves thrombin generation a little more. Addition of prothrombin improves it further, to near-normal. FEIBA, like other prothrombin complexes, provides prothrombin and factor X.

Uri Martinowitz also addressed a **surgery** issue, from a different viewpoint, namely, **how can we reduce blood loss?** His special interest is the removal of giant pseudotumors, which he has attempted only in non-inhibitor patients. He may first embolize the arterial supply. He uses anti-fibrinolytic agents, rVIIa, and, in abundance, fibrin sealants. If the entire tumor cannot be resected, he may use low-dose radiation to the remaining capsule. He says, avoid acidosis, hypocalcemia, fibrinolysis and hypothermia. The latter problem was addressed emphatically by trauma surgeon Mauricio Lynn of Miami, an appropriate speaker because removal of a huge pseudotumor is not unlike trauma surgery. Dr. Lynn says, if the operating room is comfortable for the surgeon, it's too cold for the patient. He uses a variety of techniques to warm trauma patients, including warm blankets, warming lights, warm blood and fluid, and sometimes warm lavage. Coagulation is subnormal at cool temperatures.

### Acquired factor VIII inhibitors

Julio Delgado of Madrid searched the literature, 1985-2002, and found 21 reports of series of five or more patients with auto-immune inhibitors, from 12 countries, covering a total of 234 evaluable patients. A complete remission was obtained in 74% of instances and was associated with better survival than no remission or incomplete remission. Patients with post-partum inhibitors (15% of the total) fared best, patients with malignancies (18% of the total) had the worst outcome. Patients aged more than 65 years had a significantly worse outcome than younger patients. The over-all mortality was 20%, of which 11% was related to bleeding.

He **compared treatment regimens** to the extent possible. The worst outcome was with no drug therapy. Use of cyclophosphamide was associated with a somewhat better outcome than the use of steroids alone, but cyclophosphamide was associated with a higher rate of death due to infection. (We need more reports on the efficacy of rituximab.)

Dr. Laszlo Nemes of Budapest is using **exogenous factor VIII for induction of tolerance in patients with acquired inhibitors**. He gives daily FVIII, 30 U/kg/day in the first week, 20 U/kg/day in the second week, and 15 U/kg/day in the third week, together with cyclophosphamide 200 mg/day up to a total of two to three grams and methyl prednisolone 100 mg/day, gradually tapering off. A complete remission was obtained in 24 of 26 patients, typically in four weeks. (In contrast, it took an average of 28 weeks to obtain complete remission in four of six patients he treated previously with drugs alone.) Of the 24 patients with a complete remission,

three relapsed later. Use of FVIII increases the cost of treatment. Why should addition of exogenous FVIII improve the response, after all, the patient is making his own FVIII all the time? We don't know, but his method deserves study.

### Whither coagulation testing?

Trevor Barrowcliffe described the limitations of using only the **one-stage assay** in the clinical laboratory. Its accuracy in measuring very low levels of FVIII or factor IX, that is, in predicting disease severity, troubles him, as it does me. There are a great many different sources of each reagent used, as well as many different instruments. He is particularly concerned that many laboratories assay at only one dilution of the plasma sample, and, many laboratories use duplicates instead of replicates (that is, two samples are taken from the same dilution, rather than from two separate dilutions), and, many laboratories routinely rely on standard curves stored in machines. (If a machine spews out a result, it has to be right, right? Wrong.) Many FVIII immuno-depleted plasmas may still contain a disturbing amount of FVIII, as demonstrated in thrombin generation tests.

**The thrombin generation test** (TGT) was first described in 1953, and was standard in the laboratory in which I trained in the early 1960's. It has been made easier. Dr. Barrowcliffe likes to use activated factor IX as the activating trigger and also likes a fluorogenic substrate which does away with the need for subsampling. He uses continuous recording of thrombin generation so that one can observe the lag phase and peak thrombin produced (as did Dr Roberts, in his observations on rVIIa). One can quantify thrombin generation by measuring the peak, the time to half-maximum, and area under the curve (AUC). The calibrated fluorometric method requires a special machine, which is easy to use.

One great advantage of the TGT, and the two-stage FVIII assay that was derived from it, is that very low levels of FVIII can be measured, as low as 0.1% says Dr. Barrowcliffe. My experience was, as low as 0.2% with the two-stage. (No FVIII-deficient substrate plasma is used in either system.) Dr. Barrowcliffe also notes that the recorded curve of thrombin generation becomes normal when a person with severe hemophilia A receives enough FVIII to raise his level to 30%. Does that imply that we are usually over-treating? I think so. The TGT and the thromboelastogram also can be used to follow therapy with bypassing agents. (We need to maintain good local coagulation laboratories, but, at another meeting, Sally Crudder commented that in the USA local coagulation testing abilities were withering away rather than growing.)

## Issues surrounding pregnancy

Jim Wainscoat of Oxford described progress in making **diagnoses from fetal material in the maternal circulation**. There are very few fetal cells in maternal blood, but free fetal DNA and RNA can be found and distinguished from maternal DNA and RNA, if the fetus is male. Paternally-inherited traits can be diagnosed on that fetal DNA or RNA, which is helpful for many common recessive conditions, such as thalassemia or cystic fibrosis, but not helpful for hemophilia which is maternally-inherited. Fetal nucleic acids appear very early, by day 28 of conception in 80% of instances. The major utility of testing early-appearing nucleic acids is to determine gender. In carriers of hemophilia, if the fetus is female, further tests of an invasive nature, such as chorionic villus biopsy, are avoided.

Stuart Lavery of London described **pre-implantation genetic diagnosis**, the process in which a very early embryo, formed by *in-vitro* fertilization, is biopsied. One can determine gender, look for chromosomal abnormalities and sometimes diagnose a gene disorder such as hemophilia, and then implant the healthy embryos into the uterus. He said that his patients were not seeking “designer” babies as touted in the media, instead, they had sad histories of reproductive difficulties or seriously-ill children. He emphasized the uncertainties of diagnosis with biopsy of only one or two cells from the embryo, and the uncertainties of the eventual effect of that biopsy on the children (although no ill effects have been seen so far.) Above all, he emphasized that *in vitro* fertilization is difficult, stressful and costly. Live births have resulted from only a quarter of the *in vitro* fertilization cycles in his patients. (I have been very interested in pre-implantation genetic diagnosis in order to give a carrier the hope of choosing to have an unaffected child. There have been some successes. Dr. Lavery tried to be discouraging, given the many difficulties. We can hope for progress.)

Dr. Lavery reports that **sperm separation** into X-bearing (female) and Y-bearing (male) is best with the flow cytometry method used in Fairfax, Virginia. Their outcomes are 76% success if a male is desired and 91% if a female is desired. A carrier may choose to have a daughter who may or may not also be a carrier, but for whom better answers may be available in another generation. A man with hemophilia may choose to have sons, for they will not be affected with his hemophilia.

Pier Mannucci reviewed records at his center on the **use of DDAVP during pregnancy**, other than at delivery. Concern arose because there is a slight oxytocic effect of DDAVP. Between 1988 and 2003, DDAVP in the usual dose, 0.3 micrograms/kg, was used for chorionic villus biopsy or for amniocentesis in 32 women with low FVIII (carriers or VWD patients). One dose was administered in 22 cases and two or

three in ten cases. Side effects included occasional facial flushing. Twenty pregnancies continued to term, and no problems were observed. In 12 other instances, fetuses identified as affected were aborted, under cover of additional DDAVP. No miscarriages occurred.

## The role of plasma-derived FVIII-VWF concentrate

We heard again from German investigators that **induction of tolerance** in a patient with an inhibitor may be more successful on plasma-derived FVIII (pdFVIII) with von Willebrand factor (VWF) than on purified pdFVIII or rFVIII alone. The total number of patients is not large enough for a firm conclusion, but, if a patient is not responding to tolerance induction with a product containing only FVIII, then use of a pdFVIII with VWF might be considered. Most responding patients, in my experience, have a marked fall in the inhibitor level by the end of the second month of daily FVIII. “Not responding” needs a clear definition. To me, it means no drop in the inhibitor after three months or so of therapy. Gradual decline may be a response, but whether it could be accelerated by use of FVIII with VWF is unknown.

**The German-speaking countries have an ongoing PUP surveillance project**, and, as of June 2004, are following 278 hemophilia A and 40 hemophilia B patients. The 183 hemophilia A patients who have been treated are about evenly divided between pdFVIII and rFVIII. Of those on pd FVIII, about half use FVIII with VWF and half use FVIII without VWF. Of those on rFVIII, about 80% use a product with the full-length molecule. Inhibitors have developed in 34/183 hemophilia A patients, of which 15 are high responding, 17 low, and two transient. The median exposure-days to inhibitor were 12. So far, in patients with severe and moderate hemophilia A, inhibitors appeared in 12/77 patients on pd FVIII and 21/77 on rFVIII. It seems too early to come to any conclusion.

The experience with BPL’s **pdFVIII called “8Y”**, used from the mid-1980’s until the late 1990’s, is being reviewed. **Inhibitors were infrequent**. Among 74 boys with severe hemophilia A treated solely with 8Y at five major centers, two developed a high-level inhibitor, and one developed a low-level one. Of boys tested for hemophilia mutation, 26/55 have the inversion mutation, thus they are representative of boys with severe hemophilia as a whole. The low rate of serious inhibitors, 2.7%, makes me wonder whether that concentrate was, somehow, protective. The incidence of inhibitors in the UK rose after 8Y was discontinued and rFVIII use was instituted.

Alessandro Gringeri of Italy reported on **inhibitor experience with Emoclot, the Italian FVIII-VWF concentrate** introduced there some 15 years ago. He followed 70 patients with severe and 27 with moderate hemophilia A. Of these, 30 were true

PUPs and 67 were minimally-previously-treated (that is, they had had five or fewer other blood product exposures, as is often the case with babies diagnosed outside major centers.) The rate of inhibitors is 10% among patients with severe hemophilia and none have appeared in the moderately-affected patients. The rate of inhibitors in true PUPs was 10% and in minimally-previously treated patients was 6%.

**Reports from several European countries** were put together. The **overall incidence of inhibitors developing in 302 patients treated with FVIII-VWF concentrate was 10.9%**. This was not a prospective survey, and, under-reporting of inhibitors is more likely than over-reporting, especially in retrospective reviews. The result is provocative, nonetheless, and we should keep our minds open.

### Radionucleotide synovectomy

Sometimes a new method of treatment comes along that's so beneficial, we can only say, Wow! I remember the first time I used a FVIII concentrate, the first time I used DDAVP, the first time I used Autoplex, the first patient whose inhibitor was eradicated with tolerance induction, and the first radionucleotide synovectomies done at this Hospital, all of them "wow" events. Radionucleotide synovectomy isn't new, but it has been slow to be applied around the world for hemophilic synovitis. Part of the delay is due to the nuisance and expense of getting the isotope. Even if isotope were shipped for use of just one patient, that expense, in the USA, would be well under the cost of a month of daily prophylaxis. (The Los Angeles Times reported this week that shipping isotopes by air has been further restricted. There's too much fear around.)

I was excited to hear of the **introduction of radionucleotide synovectomy over the past three years in new places**. Sylvia Thomas reported on a series of 50 patients in Cuiaba, Brazil; Yangquiang Zhao on 25 patients in Beijing, and Kaan Kavakli on 65 patients in Turkey. All reported high rates of success in suppressing synovitis. Federico Fernandez Palazzi of Venezuela, who pioneered and promoted the procedure for hemophilic synovitis, is unable to get the isotope or rifampicin (for chemical synovectomies) any more, but continues to perform chemical synovectomies with oxytetracycline chlorhydrate, called, in South America, "Emicina", from Pfizer. He has treated synovitis in 77 joints with a series of three injections at weekly intervals with generally good results, and only two failures to respond. He says, the most effective treatment for synovitis is radionucleotide synovectomy, but, Emicina is cost-effective and convenient. He comments that the ELBOW is the joint least likely to have an excellent outcome, regardless of the method of non-surgical synovectomy

### The transgenic pigs, an update

Dr. Bill Velander has been creating transgenic livestock for the past 17 years. He is now on the faculty of the University of Nebraska, in Lincoln, where there's a university-owned current-good-manufacturing-practices (cGMP) processing facility for medications. His human factor IX from the milk of transgenic pigs could be processed there for human use. His transgenic pigs remain in an isolated indoor pathogen-resistant environment in Virginia.

The human factor IX gene is transplanted into the pig ovum, *ex vivo*, together with promoters that encourage secretion into the milk of the mature sow. **The density of cells in the mammary gland is high, 1,000,000,000 per ml, more than 200 times the density of hamster cells in the cultures making recombinant products in stainless-steel vats**. His pigs produce 100 to 200 factor IX units per ml of milk.

Why pigs, why not cows-goats-sheep etc? Factor IX must be further processed in the cytoplasm. "Post-translational modification" such as glycosylation and phosphorylation, is under control of the animal's mechanisms. That of pigs is much more "human" than that of other barnyard animals.

I am most interested in the **potential for oral use** of transgenic clotting factors. Mice and dogs with hemophilia B have absorbed some of the human factor IX when it is fed in the milk of transgenic pigs. If an abundant supply is available, as from the lactating sow, absorption of a small percentage might provide enough plasma factor IX for prophylaxis. Factor IX has been the prototype. Factor VIII and other factors are being studied.

I've told this story before, I'm repeating it, to let you know that yes, it's still bubbling along. Big pharmaceutical companies have not shown an interest. Sometimes a development that's startlingly new, a different concept, is hard to launch, no matter how promising. It's easier to make a small improvement in an old concentrate and launch a big ad campaign.

### Whither gene therapy?

Don't give up. The future, says Thierry van den Driessche, includes new vectors including nano-particles containing genes, hepatocyte-specific targeting, site-specific genomic integration (to reduce the chance of exposing oncogenes), and new clotting factor molecules with improved secretion. The gene therapists haven't run out of ideas. Expense and regulations may be the limiting factors.

### Correction – recombinant porcine concentrate

In the last issue, I said, incorrectly, that Ipsen was developing a recombinant hybrid human-porcine FVIII concentrate. Not so. They've developed a recombinant B-domain-deleted porcine FVIII concentrate (not a hybrid) and it's in early clinical trials in the USA, according to Dr Garrett Bergman of Octagen Corporation of Bala Cynwyd, PA. I'm glad that a porcine FVIII will eventually be available again for those situations in which it worked so well in the past. For inhibitor patients, we need plenty of options.

### National Hemophilia Foundation, Dallas, November

I missed the sessions on **women with bleeding disorders** at WFH, but was able to catch some presentations at NHF before I was swept up into administrative meetings. Claire Philips tested some 115 women with menorrhagia for bleeding disorders. She found von Willebrand disease (VWD) in 7%, a single clotting factor deficiency in 5%, but abnormal platelet aggregation, compared to a control series, in 44%. Audience members commented that platelet aggregation abnormalities have not been well-characterized, and I agree, but that doesn't make Dr. Philips' observations any less intriguing. (I think of Harvey Weiss' observation that minor deficiencies in platelet aggregation to collagen were associated with greater bleeding tendencies in patients with borderline-mild VWD.) We really haven't learned much about platelet aggregation since I first performed it some 37 years ago. More studies of the normal population would be welcome, as well as explanations of what minor abnormalities really mean.

Variability in levels of FVIII and VWF make VWD diagnosis difficult, as Connie Miller recounted. Levels of these factors vary with the menstrual cycle. She suggests that the best time to measure levels is at the onset of menstruation, one of the points when FVIII and VWF are at their lowest, a point in the cycle that women can easily identify. Another speaker complained of the artifactually-abnormal results often returned from reference laboratories, a comment that drew loud applause from the audience.

Hematologists may receive more referrals of women for anemia than for menorrhagia, although the anemia may be caused by menorrhagia. Blood loss and iron deficiency always should be considered in anemic patients. The serum ferritin level is the best diagnostic test. Parvin Saidi, from the audience, commented that anemia may be the last sign of iron deficiency, occurring only when iron stores are well-depleted and the woman is already suffering from the effects of inadequate iron. We ought to be wary of iron deficiency in

women in the reproductive age group, especially those with menorrhagia.

Andra James reviewed the **histories of 102 women with VWD** and 88 women without bleeding disorders under the care of a gynecologist and found the following frequencies of problems:

	<u>VWD</u>	<u>Other women</u>
Menorrhagia	95%	61%
Hemorrhagic ovarian cyst	52	22
Endometriosis	30	13
Fibroids	32	17
Endometrial hyperplasia	10	1
Endometrial polyps	8	1
Hysterectomy	26	9
Miscarriages	15	9
Heavy bleeding terminating a Pregnancy	1.3	0.3
Post-partum hemorrhage	59	21

She speculated that endometriosis and fibroids might be as common in normal women as in women with VWD but are more symptomatic in women with VWD. She also commented that women with VWD were more likely than other women to have profuse bleeding with hysterectomies, needing blood transfusions.

The **treatment of menorrhagia** deserves more **controlled trials**, says Peter Kouides. There are controlled studies of anti-fibrinolytics but not of other drugs, and, especially, not of DDAVP. Tranexamic acid, licensed long ago but not marketed recently in the USA, may make a come-back, because it is a less bulky drug than EACA and may be tolerated better orally. Meanwhile some doctors are obtaining tranexamic acid in bulk from a generic manufacturer and having their pharmacies re-package it as an oral suspension.

Farewell to John Graham, who died in Chapel Hill at the age of 86, clear in his mind and vitally interested in the world around him to the end. I was never his official student but often his informal one. He was a source of frequent encouragement to me, especially in my interest in the genetics of hemophilia. He was wise in the ways of academia: his warnings to me about the "joys" of being emeritus were accurate and helpful. I shall miss him. Encouragement and friendship from senior colleagues is a great contribution to their juniors. John was a positive example to those of us who are beginning to form the senior generation.