ASTH NEWSLETTER
The Australasian Society of Thrombosis and Haemostasis

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Vol 10, No 3 December 2004

Dear Fellow Clotter

Welcome to the final edition of the newsletter for 2004. Many thanks to all the contributors, your time and input are appreciated. Much has been achieved by the society this year. In particular the inaugural Barry Firkin Oration was given by Michael Berndt on the education day of the annual scientific meeting. Included in this edition is a synopsis of Michael's presentation and some background on the Barry Firkin award designed and created by Nick Mount an artist from Adelaide.

Congratulations to Quintin Hughes (University of WA/Royal Perth Hospital) who won the AstraZeneca Medal and the $2000 prize at the recent HAA in Melbourne. Runners up (Jenny Curnow and Scott Dunkley) both received $500 and all winners were presented with certificates.

Linda Williams from AstraZeneca presenting Quintin Hughes with his prize.

The warfarin reversal consensus guidelines (on behalf of the ASTH) were announced during the HAA in Melbourne, a summary and details on their publication are provided. Tim Brighton has supplied all the important information regarding the upcoming ISTH to be held in Sydney in August next year. Also included are reports on the ASTH Coagulation Workshop held at the Alfred Hospital, the HAA in Melbourne and the World Federation of Hemophilia Congress held recently in Bangkok.

Included in this edition is news from the Secretariat, the New and Emerging Technologies Group and details of the ASTH Travel Grant winners. Please find enclosed along with the newsletter a copy of the Presidents Report and the Treasurers Report presented at the recent AGM.

It was great to meet so many of you in Melbourne recently, thankyou for your support.

Another 3 issues of the newsletter are planned for 2005. Contributions are most welcome.

Merry Christmas and hope you have a safe and happy New Year

Emma Perrin

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THE INAUGURAL PROFESSOR BARRY FIRKIN ORATION: "RISTOCETIN, WHAT HAVE WE LEARNT"

by Michael C. Berndt
Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria, 3800

In the 1970s, the promising and effective vancomycin family antibiotic, ristocetin, from N*ocardia lurida*, was withdrawn from human use because of an unexpected pro-thrombotic effect – an effect not apparent in animal trials. To his everlasting credit, Professor Barry Firkin and his colleagues at Monash University in Melbourne did not simply dismiss ristocetin as a failed, commercially nonviable drug, but investigated the molecular mechanism underlying its pro-thrombotic activity. The consequences of this far-sighted decision have resonated in the haemostasis and thrombosis field for over thirty years. Ristocetin, it was subsequently found, causes platelet aggregation by specifically inducing binding of von Willebrand factor (VWF) in plasma to its receptor, the glycoprotein (GP)Ib-IX-V complex on platelets. The interaction of platelet GPIb-IX-V and VWF multimers in plasma, or associated with the vessel wall (subendothelial matrix or bound to activated endothelial cells), is critical to initiation of platelet aggregate (or thrombus) formation at high shear stress in flowing blood. I*n vivo*, this interaction is only triggered by injury exposing subendothelial matrix (activating immobilized VWF) or by pathological shear stress in a stenotic blood vessel (inducing plasma VWF-GPIb-IX-V interaction). Ristocetin-dependent binding of VWF to platelet GPIb-IX-V inducing platelet aggregation under stirring conditions *in vitro* directly mimics this shear-dependent adhesion. It has made a fundamental contribution to understanding haemostasis/thrombosis in three important ways: first, ristocetin-dependent platelet aggregation is a long-standing diagnostic test of patient VWF- and/or GPIb-IX-V-dependent platelet function; second, ristocetin is extensively employed as a research tool for dissecting the molecular interactions involved in ligand-receptor recognition, through analysis of control or mutant patient samples, inhibitory antibodies against VWF or GPIb alpha-chain (the ligand-binding subunit of GPIb-IX-V), or of cross-species GPIb chimaeras; and third, the analysis of the ristocetin-recognition site on the VWF A1 domain led to the identification of a proline-rich sequence (DLAPEAPPPTLPP) flanking A1 as an important regulatory site in activation of VWF. Peptides containing the proline-rich sequence of human VWF bind to ristocetin, although not necessarily at the same site as that recognising the bacterial cell wall D-Ala-D-Ala dipeptide sequence. Notably, the predilection of ristocetin for recognition of VWF in humans, but not other species such as mouse, rat, pig or dog, for example, where the proline-rich sequence is poorly conserved, has provided a unique approach to analysis of human platelet GPIb function. In contrast to ristocetin, other non-physiological modulators of VWF such as the snake toxin, botrocetin (a C-type lectin-family protein) act promiscuously across species *via* a mechanism distinct from that of ristocetin. Thus, comparing ristocetin-dependent *versus* botrocetin-dependent VWF binding to cross-species chimaeras of GPIb expressed on CHO cells has revealed precise functional sites mediating patho/physiological thrombus formation, results confirmed under conditions of hydrodynamic flow. Further, in 2003-2004, the first crystal structures of VWF-A1 in complex with the ligand-binding fragment of GPIb have begun to explain the molecular basis for how this interaction is mediated, and how ristocetin binding to VWF (or GPIb-IX-V) could cause the platelet aggregation that frustrated the early applications of ristocetin as an antibiotic. Together, these diverse studies stemming from the prescient and careful observations of Professor Firkin have had a profound effect on current understanding of human thrombosis relevant to heart attack and stroke. The original curiosity which inspired them remains a salient lesson for present day investigators in biomedical research.

Michael Berndt and Hatem Salem.

THE BARRY FIRKIN ORATION AWARD

Nick Mount is one of Australia's pre-eminent glass artists. He is recognized for his commissions, teaching and exhibitions in Australia, Europe, South America, the United States and Japan and his work is represented in many major public and private collections.

Nick's idea was to create a heavy walled glass tube with a 'flash' of red glass on the inside of the tube. The tubular form refers to the nature of Professor Firkin's work and the nature of the glass itself while the ends of the tube were cut and polished to reflect the precision of the sciences. The curving, overlapping shape of the bent tube is a cradling and nurturing form which describes Professor Firkin's care for his work, peers and patients. Each piece will be individually created without the use of moulds or tools and will therefore be unique in its shape and size.

Ruth Firkin presented Michael Berndt with the first Barry Firkin Oration Award.

SECRETARIAT NEWS

Dear Members,

It was nice to catch up with all the usual suspects again and to meet some new people at the conference in Melbourne in October. Hopefully next year we will be able to have a booth so people don't confuse me with the information desk...

It would be fantastic if some of the ASTH nurses could contribute papers to the meeting in Sydney next year. There are always some great presentations at the Nurses' Education Day, but rarely anything from the thrombosis nursing/clinical trial nursing contingent. Perhaps keep this idea in mind when abstracts are called for next year?

New Members

The ASTH welcomes the following new members:

ABDALLAH, Dr Alhossain
Royal Adelaide Hospital, Adelaide

ALLAN, Mrs Karen
Canterbury Health Laboratories, Christchurch, New Zealand

BIRD, Dr Robert
Prince Alexandra Hospital, Woolloongabba, Queensland

COLEMAN, Ms Cheryl
Monash Medical Centre, Clayton, Victoria

COLEMAN, Ms Robyn
Sullivan Nicolaides Pathology, Indooroopilly, Queensland

CUMMINS, Ms Anita
Monash Medical Centre, Clayton, Victoria

CURNOW, Dr Jenny
Royal North Shore Hospital, St Leonards, New South Wales

HAUGHTON, Dr Anne
Mater Hospital, South Brisbane, Queensland

HO, Dr Wai Khoon
Royal Perth Hospital, Perth, Western Australia

HUGHES, Mr Quintin
Royal Perth Hospital, Perth, Western Australia

RUDDENKLAU, Ms Anna
Canterbury Health Laboratories, Christchurch, New Zealand

SIMMANCE, Dr Andre
Monash Medical Centre, Clayton, Victoria

STAFFORD, Mrs Lynnette
Monash Medical Centre, Clayton, Victoria

WOODBURN-DENNIS, Mrs Robyn
Melbourne Pathology, Collingwood, Victoria

Membership renewals have been emailed (and posted) recently for 2004/2005 along with individual listings for the new membership booklet. If you did not receive a listing, it means you did not give your permission for your details to be included in the booklet. So if you change your mind and you would like to be listed, please phone or email me to arrange. Could you please try and return both of these forms to me by the due date, which is 3rd December.

Have a great Christmas.

Leonie

ISTH SYDNEY 2005 UPDATE

The XXth Congress of the International Society on Thrombosis and Haemostasis (ISTH) and the 51st Annual SSC meeting will be held in Darling Harbour Convention Centre in Sydney on 6-12th August 2005. For those unfamiliar with this meeting this is the big one – a biennial meeting on Thrombosis and Haemostasis and related disciplines. The XXth Congress is notable as the first south of the equator and also for being in Sydney so readily accessible to ASTH members. The themes for the congress include:

- Coagulation Factors and Inhibitors
- Fibrinolysis, Fibrinogen, Fibrin, Factor XIII
- Haemorrhagic Disorders
- Innovation and Technology
- Platelets
- Thrombotic Disorders
- Vascular Biology

This is a meeting not to be missed. Everything you need to know is available on the website at *www.isth2005.com* for registration, abstract submission (now open), booking accommodation and an updated scientific program. The social program is excellent and includes an innovative Opening Ceremony on Sunday 7th at 17:30pm, a Congress Opera at one of the worlds great opera venues (Verdi's Nabucco) on Tuesday 9th August, and a informal fun-packed Congress Party on Thursday 11th at 19:00pm.

Key dates are

Abstract Submission Deadline
14 January 2005

Notification of acceptance of abstracts
April / May 2005

End of early bird registration fee
31 May 2005

Accommodation Booking Deadline
25 June 2005

ISTH2005 Congress
6-12 August 2005

The AstraZeneca Medal Winner:

Quintin Hughes, University of WA/Royal Perth Hospital "Oestrogen Regulation of the Anti-coagulant Protein S."

Runners up:
Jenny Curnow, Royal North Shore Hospital "Identifying hyper-coaguable states with a simple global coagulation assay: the overall coagulation potential"
Scott Dunkley, Prince of Wales Hospital "Tirofiban induced thrombocytopenia is associated with drug dependent antibodies that cause platelet activation and increased ischaemic events".

WARFARIN REVERSAL: CONSENSUS GUIDELINES, ON BEHALF OF THE AUSTRALASIAN SOCIETY OF HAEMOSTASIS AND THROMBOSIS

In 2002 Gallus *et al* (1) published consensus guidelines for warfarin therapy including general recommendations on situations where warfarin reversal may be required. However, there remains considerable uncertainty among treating doctors about when warfarin anticoagulation should be reversed and which methods should be used. There is also significant variation in the approach to reversal of warfarin peri-operatively and the use of bridging anticoagulation. This arises, in part, because there are no randomised, controlled clinical trials to guide practice and recommendations are based on small observational studies or extrapolation from related clinical situations. The ASTH therefore established a consensus group of haematologists to review the literature and, in the light of their combined clinical experience, to produce a set of recommendations specifically for warfarin reversal (2). The guidelines were produced for a general target audience of general practitioners, emergency physicians, surgeons and junior medical staff.

The consensus statement included suggestions on appropriate use of vitamin K (oral or IV) and clotting factor replacement (FFP or prothrombin complex concentrate). The group noted that the use of small doses of vitamin K in patients with significant over-anticoagulation usually returns the INR to a safe level without inducing warfarin resistance. The use of prothrombin complex concentrate (Prothrombinex-HT) was encouraged in situations where rapid and complete reversal of anticoagulation was required, especially where large volumes of FFP are inappropriate (eg intracranial haemorrhage or co-existing heart disease). Because prothrombin complex concentrate (Prothrombinex-HT) is a three factor preparation (prothrombin, IX and X) it was recommended that FFP (150-300ml) be given in addition as a supplementary source of Factor VII.

Table 1 shows recommendations for warfarin reversal when the INR is elevated either with or without clinically significant bleeding. It should be noted that the recommendations allow considerable latitude in the requirement for rapid reversal depending on the presence or absence of additional risk factors for bleeding. They also emphasise the need for careful clinical follow up and re-testing of the INR to ensure that the required outcome (therapeutic INR or complete reversal) has been achieved.

In the case of peri-operative management of warfarin and the use of bridging anticoagulation the consensus group recognised that evidence was limited but felt it was appropriate to consider management of low and high risk situations. Patients receiving warfarin for atrial fibrillation without other risk factors or long term secondary

Table 1. Guidelines for the management of an elevated international normalised ratio (INR) in adult patients with or without bleeding

Clinical setting	Action
INR higher than the therapeutic range, but <5.0, bleeding absent	• Lower the dose or omit the next dose of warfarin. Resume therapy at a lower dose when the INR approaches therapeutic range. • If the INR is only minimally above therapeutic range (up to 10%), dose reduction may not be necessary.
INR 5.0-9.0,* bleeding absent	• Cease warfarin therapy; consider reasons for elevated INR and patient-specific factors. • If bleeding risk is high, give vitamin K1 (1.0-2.0 mg orally or 0.5-1.0 mg intravenously). • Measure INR within 24 hours,† resume warfarin at a reduced dose once INR is in therapeutic range.
INR >9.0, bleeding absent	• Where there is a low risk of bleeding, cease warfarin therapy, give 2.5-5.0 mg vitamin K1 orally or 1.0 mg intravenously. Measure INR in 6-12 hours, resume warfarin therapy at a reduced dose once INR <5.0. • Where there is high risk of bleeding,‡ cease warfarin therapy, give 1.0 mg vitamin K1 intravenously. Consider PROTHROMBINEX-HT (25-50 IU/kg) and fresh frozen plasma (150-300 mL), measure INR in 6-12 hours, resume warfarin therapy at a reduced dose once INR <5.0.
Any clinically significant bleeding, where warfarin-induced coagulopathy is considered a contributing factor	• Cease warfarin therapy, give 5.0-10.0 mg vitamin K1 intravenously, as well as PROTHROMBINEX-HT (25-50 IU/kg) and fresh frozen plasma (150-300 mL), assess patient continuously until INR <5.0, and bleeding stops. OR • If fresh frozen plasma is unavailable, cease warfarin therapy, give 5.0-10.0 mg vitamin K1 intravenously, and PROTHROMBINEX-HT (25-50 IU/kg), assess patient continuously until INR <5.0, and bleeding stops.§ OR • If PROTHROMBINEX-HT is unavailable, cease warfarin therapy, give 5.0-10.0 mg vitamin K1 intravenously, and 10-15 mL/kg of fresh frozen plasma, assess patient continuously until INR <5.0, and bleeding stops.§

* Bleeding risk increases exponentially from INR 5 to 9. INR ≥ 6 should be monitored closely. † Vitamin K effect on INR can be expected within 6-12 hours. ‡ Examples of patients in whom the bleeding risk would be expected to be high include those with active gastrointestinal disorders (such as peptic ulcer or inflammatory bowel disease), those receiving concomitant antiplatelet therapy, those who underwent a major surgical procedure within the preceding two weeks and those with a low platelet count. See Box 1 for a list of bleeding risk factors. § In all situations carefully reassess the need for ongoing warfarin therapy.

prophylaxis for venous thrombo-embolism are likely to be at low risk. Patients with recent significant thrombo-embolism (<3 months) or prosthetic heart valves are more likely to be at high risk of peri-operative thrombosis. Recommendations for bridging anticoagulation are shown in Table 2. The guidelines emphasise the importance of clinical assessment of the individual patient with respect to their risk of thrombosis versus bleeding and the involvement of relevant specialists in the decision making process. It was also noted that many patients on warfarin can have procedures such as minor skin surgery and simple dental work performed without any warfarin reversal provided that the INR is not elevated above the therapeutic range.

References.

1. Gallus AS, Baker RI, Chong BH et al. Consensus guidelines for warfarin therapy. MJA 2002; 172:600-605.
2. Ross Baker, Paul Coughlin, Alex Gallus, Paul Harper, Hatem Salem and Erica Wood. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Haemostasis and Thrombosis. MJA 2004; 181:492-497.

Table 2. Managing oral anticoagulation during invasive procedures according to risk of thromboembolism

Time	Patients at relatively low risk	Patients at relatively high risk
Before surgery	• Withhold warfarin therapy 4-5 days before surgery. • ***Night before surgery:*** If INR >2, give 1-5 mg vitamin K1 intravenously. • ***Day of surgery:*** If INR ≤ 1.5 surgery can proceed. If INR >1.5, defer surgery, or if surgery is urgent, give PROTHROMBINEX-HT (25-50 IU/kg) plus 150-300 mL fresh frozen plasma or 10-15 mL/kg of fresh frozen plasma if PROTHROMBINEX-HT is not used.	• Withhold warfarin therapy 4-5 days before surgery. • ***2-3 days before surgery:*** Start giving daily or twice-daily treatment doses of unfractionated heparin intravenously or low molecular weight heparin (LMWH)* subcutaneously. • If using LMWH, the last dose (maximum dose of enoxaparin 1mg/kg or dalteparin 100 U/kg) should be at least 24 hours before surgery. If using unfractionated heparin, it should be discontinued 4-6 hours before surgery.
After surgery	• Start warfarin therapy on the day of surgery, at the previous maintenance dose. • Employ thromboprophylaxis as per usual practice.	• Recommence warfarin therapy as soon as possible. • Start heparin or LMWH 12-24 hours postoperatively. • If using LMWH, give a thromboprophylactic dose. • If using unfractionated heparin, aim to prolong the APTT by 1.5 times. • Fully anticoagulate the patient 72 hours postoperatively as long as there is no evidence of bleeding. • Cease heparin or LMWH therapy 48 hours after the target INR is reached.

INR = international normalised ratio. APTT = activated partial thromboplastin time.
* Exercise caution in patients with impaired renal function (calculated creatinine clearance, <30 mL/hour). LMWH can accumulate and contribute to bleeding.

2004 HAA ANNUAL SCIENTIFIC MEETING

The 2004 HAA Annual Scientific Meeting was held in Melbourne from the 17th-20th Oct, at the Melbourne convention centre. Over 800 delegates attended a diverse conference containing material from a broad range of disciplines with a mix of local and international speakers. This year saw the addition of a new programme with presentations directed towards issues within the diagnostic laboratory. Sessions covered a range of issues such as practical issues with tissue banking, paediatric reference ranges, laboratory tests for HIT, thrombophilia testing and blood film morphology. Working in a specialist haemostasis laboratory the morning session 2 – 'The Cutting Edge' was of particular interest.

The presentation by Beng Chong discussed the laboratory tests used in testing for Heparin-induced thrombocytopenia (HIT). Laboratory tests can be split into functional tests and immunoassays, with the importance of laboratory testing increasing when the clinical picture is uncertain. Functional tests are technically more difficult but measure HIT antibodies that are more clinically relevant. Whereas, immunoassays are technically easier and more sensitive, but do detect clinically irrelevant antibodies in some patients. Recommendations were for hospital laboratories to use immunoassays and referral laboratories to perform both functional and immunoassays.

The following presentation by Paul Ockelford outlined some important issues in the area of thrombophilia testing. Highlighting that the presence of a blood test marker does not independently define a person as having thrombophilia. The rational on 'who to test', 'why to test', and 'who not to test' was also discussed leading to some interesting discussion questions.

Overall the conference catered for everyone and the addition of the diagnostic laboratory programme was a popular choice producing positive feedback and many topics for discussion.

Karen Allan

NEW AND EMERGING TECHNOLOGIES GROUP REPORT

The ASTH Workshop was recently held at The Alfred Hospital on Saturday 16th October, to coincide with the 6th HAA Scientific Meeting in Melbourne. The Workshop was well supported with 86 attendees listening to a variety of talks in three sessions; New and Emerging Technologies, Overviews and Updates and Case Studies. A more detailed report is provided in this newsletter from Sarah Just. Many thankyous have already been distributed, but Emma and I would especially like to thank the speakers for providing their time, knowledge and experience to the Workshop, everyone who attended for supporting the event and to Hatem Salem and Jennie Saravanamuttu for organising catering and the venue for the Workshop. I hope that everyone attending the Workshop found something worthwhile from the experience.

A questionnaire was distributed at the end of the Workshop to reflect on the Workshop and to assist in planning for future events. From 61 responses, the feedback was generally very positive with most people satisfied with the organisation and content of the Workshop. Some of the interesting outcomes from the questionnaire were:

- 75% of attendees were more likely to attend the HAA Scientific Meeting if a similar ASTH Workshop were to be held in conjunction with future scientific meetings.
- 92% of attendees indicated that an ASTH Workshop should be held each year.
- 82% of attendees indicated that an ASTH Workshop should be held the day prior to the start of the HAA Scientific Meeting.
- Of those who were non-members of the ASTH (n=31), 48% indicated that they would now become a member of the ASTH and 65% indicated that they would become a member of the ASTH if a Workshop were to be held each year.

Other news from the New and Emerging Technologies Group:

- A report on NET Group activities during 2003-04 was tabled at the ASTH AGM during the HAA Scientific Meeting.
- Due to the ISTH meeting being held in Sydney next August, Council has decided not to organise and run an ASTH Workshop in 2005. This decision was made on the basis that it would be perceived to be in direct competition with the ISTH program and satellite meetings, which will also include a meeting directed at laboratory scientists (more details to follow via email when available) and that there are already sufficient Workshop style events e.g. AIMS Workshops to be held in Sydney. A Workshop in 2006 will remain on the agenda for the Hobart HAA.
- The NET e-newsletter will be incorporated into the main newsletter of the society. The ASTH newsletter will now contain a greater emphasis on laboratory and diagnostic science to aid this streamlining of correspondence.

Wishing everyone a safe and fun festive season.

With warm regards,

Murray Adams
Chair

UPCOMING MEETINGS

MEETING	WHERE/DATES	CONTACT
International Symposium on Women's Health Issues in Thrombosis and Haemostasis	Budapest 4-6 February 2005	www.kenes.com/whith
RCPA Pathology Update	Sydney 11-13 March 2005	Suzanne Marks Phone: 61 2 8356 5806 www.rcpa.edu.au/pathologyupdate
10th International Myeloma Workshop	Sydney 10-14 April 2005	Myeloma 2005 Workshop Managers Tel: 61 2 9248 0800 www.myeloma2005.org
45th British Society of Haematology ASM	Manchester 11-13 April 2005	www.b-s-h.org.uk
XVIIIth International Symposium on Technological Innovations in Laboratory Haematology	San Francisco 11-14 May 2005	www.islh.org
AIMS National Scientific Meeting	Sydney 6-8 July 2005	www.aims.org.au
XXth Congress of the International Society of Thrombosis & Haemostasis (ISTH 2005)	Sydney 6-12 August 2005	www.isth2005.com
XXX. World Congress of The International Society of Hematology. ISH2005	Istanbul 28th Sept-2nd Oct 2005	www.ish2005istanbul.org
HAA 2005 Annual Scientific Meeting	Sydney 16-19 October 2005	haa2005@fcconventions.com.au

ASTH WORKSHOP MELBOURNE 2004

A drizzly Melbourne morning heralded the start of the 2004 ASTH Haemostasis Workshop held at the Alfred Hospital. The workshop was held the day before the 6th Joint Scientific meeting of the HSANZ, ANZSBT and ASTH. The program was divided into three sessions: New and Emerging Technologies, Overviews and Updates and Case studies.

The morning session included talks from Karen Allan, Canterbury Health Laboratories, on their experience with implementation of a FVIII binding assay, to assist in diagnosis of Type 2N vWD in the New Zealand population. They have identified 29% of patients with reduced FVIII binding who might otherwise have been misdiagnosed as Haemophilia A or type I vWD. Richard Olsen, Helena laboratories, gave an entertaining presentation on "What is (The) Point of Care?" Richard presented slides on the differences between pathology laboratories now and 40 years ago, why point of care is popular to clinicians due to the changes such as remoteness of labs, batching of tests increased numbers of tests performed, computer technology and delays in producing results. The industry is now targeting point of care (POC) instruments to the medical staff with this in mind. The worldwide market for POC was US$3.3 billion in 2002 and expected to grow by 8% annually. He concluded with the question – "Should the pathology laboratory be involved in these changes?"

Alessandra Bianchi, Concord Hospital, presented an overview of their experience with the ROTEM analyser in burns patients. The ROTEM analyser, is based on the principles of thromboelastography, and has the ability to look at thrombin formation, platelets and fibrinolytic parameters all in the one test system. Janice Woods, Beckman Coulter, then took us on a tour of high throughput SNP/2D Protein fractionation and its application in identifying protein expression in disease and non-disease states. Geoff Kershaw, Royal Prince Alfred Hospital, described the development and processing of samples in the ADAMTS-13 activity assay that they are performing in their laboratory. ADAMTS-13 (von Willebrand factor cleaving protease) deficiency (<5%) has been identified as a key laboratory finding confirming the diagnosis of thrombotic thrombocytopenic purpura (TTP). The test can take from 5-8 days to complete and involves the first step of placing purified vWF and patient samples on to filters overnight and allowing cleavage of vWF by the ADAMTS-13 under denaturing conditions. The product is carefully removed from the filter and then processed for multimer electrophoresis. The current method is good but some technical issues need to be resolved, one option is to use the collagen binding assay rather than the multimer assay to test samples after vWF cleaving. Thomas Exner, St Vincent's, Sydney and Haematex Research Lab then gave an interesting presentation on the XACT test for assessing platelets and microparticles. Procoagulant phospholipid (PPL) is an essential component for several haemostatic processes but at present can not be measured by any current laboratory tests. PPL is provided at sites of injury by activated platelets and increased levels occur whenever platelets are activated (ie autoimmune disease, thrombosis, HITTs etc) which can be measured by flow cytometry. The factor Xa activated clotting time (XACT) test is particularly sensitive to shortening by PPL, and can be run on any coagulation analyser capable of running PT tests. Using this test they have confirmed elevated levels of PPL in patients with ischaemic heart disease.

Lunch followed in the offices of the Haematology Research section at the Alfred with views of the surrounding suburbs. The afternoon session comprised of presentations from Kate Maslen, Royal Perth Hospital, on trends in anticoagulation: pentasaccharides. Kate discussed the current clinical trial data on fondaparinux and idraparinux, both indirect Xa inhibitors and their efficacy in the prevention of venous thromboembolism. Tim Brighton, St George Hospital, gave a presentation on new anticoagulants focussing on the direct thrombin inhibitor ximelagatran. Clinical studies on this drug look promising. The FDA committee ruled that if the hepatotoxic effects of exanta could be resolved then with the demonstrated efficacy in clinical trials it could be considered as an alternative to warfarin therapy. Thomas Exner gave his second presentation for the day on APTT's and related assays. He discussed the variables associated with different APTT reagents used in today's laboratories highlighting the differing sensitivities to contact factors. A new "Splitmix" method now offers alternatives to identifying contact factor defects and inhibitors, by preincubating test plasma with APTT reagent and then adding a complementary plasma before recalcifying. He suggested labs carefully consider their clinical needs when choosing APTT reagents. Stacey Harbour, Austin Research Institute, presented her research findings on dissecting integrin (IIb (3 signalling defects in platelets. Ray Dauer, Austin Hospital, presented an evaluation method using ROC analysis in which they tested three different commercial anti B2 glycoprotein assays. He suggested careful analysis of data when evaluating test systems to ensure that the kit provides appropriate discrimination of results for your patient population. Paul Monagle, Royal Children's Hospital Melbourne, gave two presentations the first on age related reference ranges in haemostasis and the implications for clinical care. Paul's laboratory has developed age specific reference ranges for the Stago system of coagulation analyser and reagents, using 400 healthy children and 120 healthy neonates. His next presentation was a case of homozygous plasminogen deficiency in a baby with sticky eyes. Histology of the excised membranous conjunctivitis showed fibrin and heparin eye drops were commenced. Further surgery has been required on one eye with the other resolving with eye drops. Homozygous plasminogen deficiency was confirmed by blood tests. All five siblings and parents were tested and one other sibling a 7 year old girl also had levels <10%, but displayed no symptoms.

The afternoon session on "Case studies" had several very interesting presentations. Mark Williams, Mater Hospital, Brisbane presented two cases the first titled "Haemophilia? Ah?" A nine day old male with non-stop bleeding following a heel prick was found to have FVIII levels of 12%. Family studies were performed and both parents tested normal. The diagnosis was made of a spontaneous FVIII mutation leading to Haemophilia A. Marks second case presentation was titled "Something Fishy". A 63 year old female with a history of bleeding and a diet high in fish (tuna) and fish oil tablets

continued overleaf

ASTH WORKSHOP MELBOURNE 2004 *Continued*

2-3 times daily. All coagulation tests were normal, the platelet function testing (PFA100) and platelet aggregation studies were abnormal and consistent with an aspirin like defect. The patient ceased fish oil tablets and two weeks later a repeat PFA and aggregation studies were normal. The previous abnormal results being attributed to the fish oil consumption. Trish Walker, Austin Health, presented of a case of a FVIII inhibitor, seen in their laboratory and stressed the importance of investigating prolonged APTT's with mixing studies and consulting with clinicians. Robyn Coleman, Sullivan and Nicolaides Pathology, Queensland presented two cases of acquired von Willebrands syndrome that their laboratory has seen this year. Incidence is reported as 0.04-0.13% of general population. Patients present with bleeding symptoms similar to congenital vWD and it is caused by decreased synthesis or increased destruction, often immune mediated or mechanical destruction of the higher molecular weight multimers.

Congratulations to the NET group of the ASTH for a great scientific workshop focusing on new and emerging technologies, overviews and updates and interesting case studies in the world of haemostasis.

Sarah Just

REFLECTIONS FROM BANGKOK

The Twenty Sixth International Congress of the World Federation of Hemophilia (WFH) was held in Bangkok, exactly coincident with the ASTH meeting in Melbourne. This was only the second time that this biennial meeting had been held in Asia. It is a very different kind of meeting from most that we attend. It is much more multi-disciplinary with patients, nurses, allied health and multiple medical and surgical specialists (reflecting the huge diversity of clinical problems of haemophilia) regulators and other government employees attending, together with representatives from industry.

WFH has one hundred and one national member organisations throughout the world and others with 'associate' affiliation. A patient's access to haemophilia diagnosis and treatment varies according to their country's gross national product and commitment and ability to fund haemophilia programs. Patients and treaters from all around the world attend the congress.

The program reflected both similarities and differences in the models of care adopted and adapted in many countries consequent on funding. The similarities are the need for accurate laboratory diagnosis and registration of patients with bleeding disorders and access to safe product. The differences are in the amount of replacement product made available to progressively supply patients' needs for emergency care, routine surgery, prophylaxis and inhibitor suppression.

Many simultaneous sessions are convened by special interest committees, such as musculo-skeletal, laboratory etc. In the medical program there was further exploration of the major unresolved issue, as to the risk of allo antibody (inhibitor) emergence, dependent on the type of product (plasma vs Recombinant) and timing of first dose in infancy and which is the better product type to suppress inhibitors, once developed. A large multinational study is underway to address the second uncertainty.

Talks on genetic strategies from defect detection to potential cure of the disease always attract great interest and have been summarised by John Rowell (for publication in next newsletter). There was a welcome focus on laboratory issues.

There were also many updates on blood safety issues, including the emerging threat of prion disease, and on epidemiology, progression and management of blood borne infections (especially co-infection of Human Immuno-deficiency Virus and Hepatitis C infection).

Other sessions addressed regulatory and other strategic issues of interest to government. Haemophilia care is very costly particularly in the emerging era of recombinant products ("for all" in more fortunate countries and since October 1st 2004 in Australia) and with implementation of extensive prophylaxis and inhibitor suppression programs. There were talks on cost-effectiveness and evidence based practice. There is remarkably little data published in this area though the Cochrane collaborators have now started to trawl the archives and make recommendations for future studies.

It has long been known (and continues to be the case) that patients with haemophilia who are managed through a haemophilia centre have much better treatment outcomes and reduced mortality than those treated outside centres. Recruiting haematologists to manage such centres in the era of cellular therapies and bone marrow transplantation is a worldwide problem because of lesser remuneration and professional interest. Many haemophilia centres have developed thrombosis programs – a trend, which is already variably adopted in Australia and New Zealand. Almost as a victim of the successful advocacy in obtaining plentiful safe replacement product, patients are dependent on their centres far less of the time and for "unusual" events rather than the usual bleeds. Haemophilia patient organisations are aware of the need for 'eternal vigilance' in maintaining high clinical standards and they are alert to the possible threats to the viability of stand-alone specialty centres. They are starting to embrace the need for diversification.

Whilst in Bangkok although we were missing the scientific stimulation of ASTH – we gained satisfaction in being part of the global community of blood safety and haemophilia care experts working with their patients to help them aspire to more normal lives.

Alison Street

(Reference:Haemophilia Vol. 10, Supplement 4, October 2004. State of the Art XXVI in International Congress of the World Federation of Hemophilia).

2004 *Travel Grant Winners*

Three grants, each of A$1,000 were awarded

Karen Allan, Canterbury Health Laboratories
"Activated Seven Lupus Anticoagulant method Development"

Murray Adams, Curtin University
"The Tissue Factor Pathway in Ischaemic Stroke Patients"

Kate Maslen, Royal Perth Hospital
"Measurement of Soluble P-selectin and Soluble CD40 Ligand in Serum and Plasma"