ASTH NEWSLETTER
The Australasian Society of Thrombosis and Haemostasis
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Dear Fellow Clotter

Welcome to the final edition of the newsletter for 2006. In this issue you will find reports from the new and emerging technologies group and the clinical trials group as well as details of the ASTH Travel Grant winners for 2006 and the upcoming meetings for 2007. Included also are conference reports from the recent ASM and workshop in Hobart, the Asian Pacific Congress held in China and the AIMS/AACB national meeting also held in Hobart.

Congratulations to Jennifer Curnow (Royal North Shore Hospital) who won the ASTH Medal and the $2000 prize at the HAA in Hobart. The runners up (Jeremy Roberts and Quinton Hughes) both received $500 and all winners were presented with certificates. Jennifer's abstract is included in this edition of the newsletter. Professor Ted Tuddenham gave the Barry Firkin Oration in Hobart this year and Mark Smith has written an overview of his presentation.

Our secretariat has recently taken leave for twelve months. Megan has written a short piece explaining what she will be up to while away. Welcome to Vicky Mrowinski who will be the ASTH secretariat until November 2007.

One final note, I would like to make special mention of the excellent job Murray Adams performed on the day of the Hobart workshop (and late into the evening before) to keep everything running smoothly, not an easy task.

Thank you to all the contributors – your efforts are appreciated a great deal. Merry Christmas and I hope you have a safe and happy New Year.

Emma Perrin

SECRETARIAT NEWS

Having been with the ASTH for just one year I am fortunate to have been granted 12 months leave. During this period I will be travelling to Ethiopia with my husband and four children. My youngest daughter is adopted from Ethiopia and we thought that it would be a wonderful experience for our family to learn more about her birth culture. We will all be attending a local school, the children as students and both my husband and myself as teachers (fortunately for all of us the lessons are in English). At this stage I've been assigned to the Kinder class but this may change!

With an interest in haemophilia from my other position with the Australian Haemophilia Centre Directors' Organisation I hope to make contact with some clinicians in Addis Ababa and perhaps facilitate a connection with the World Federation of Haemophila – at the moment Ethiopia is not a member of the WFH and there is a very limited capacity to diagnose let alone treat inherited bleeding disorders.

I will be returning to the ASTH in November 2007 and look forward to working with you all again then.

Megan Sarson-Lawrence

INVITATION TO ATTEND GOLD COAST HAA 2007

Next year the annual meeting will be held at the Gold Coast Convention and Exhibition Centre from the 14 - 17 October 2007. The ASTH council has decided to increase the number of travel grants awarded next year to six, each worth $1000 and there will be two poster awards, best poster clinical and best poster laboratory. Also the age for eligibility to nominate for the ASTH best scientific presentation award has been increased to 45 years.

Abstract submission closes July 2007.

The organising committee is working hard to come up with an appealing program and with thirteen international speakers already confirmed we are well on the way.

For further details of the invited speakers visit *www.fcconventions.com.au*/HAA2007/.

The conference dinner on the Tuesday night is at Sea World… see the polar bears or bring the kids and enjoy the rides. So, apart from the obvious educational benefits take time to consider heading north for a few extra days.

Emma Perrin

ASTH TRIALS GROUP REPORT

The ASTH CTG continues to support investigator initiated projects. The ASPIRE (*http://www.ctc.usyd.edu.au/trials/other_trials/aspire.htm*) study continues to gradually recruit patients. This study examines the benefits of low-dose aspirin as prophylaxis against recurrent venous thrombosis after initial warfarin therapy in patients with unprovoked DVT or pulmonary embolism. There are now 320 patients enrolled from 39 actively recruiting sites. Nearly 20 sites have not recruited a patient for the last 3 or more months which is disappointing. The Trial Management Committee continues to work behind the scenes to improve recruitment, secure more funding for the study, and to open new sites. Singapore has received ethics approval and sites in India and the UK have expressed interest in the study. The companion study in Italy, the WARFASA Study, has now recruited about 180 patients.

A sub-study of the ASPIRE study, the PREDICT study, will be examining the ability of residual thrombus, plasma D-dimer, and other clinical and laboratory parameters to predict late recurrence of vein thrombosis. The final protocol has received ethics approval at University of Sydney and will be distributed to interested sites soon. We were interviewed by the National Heart Foundation (15th August 2006) and are optimistic they will look favourably on our request for support.

An almost complete protocol for the randomised study of oral dexamethasone versus oral prednisone for acute initial therapy of adult ITP, the ASTH ITP1 study, was distributed by email during July. Very few comments and responses to participate in the pilot study have been received. The plan is to proceed with this study at as many sites as possible and to make the study very focused on the primary question given the inability to raise any industry support for the study.

Investigators and sites with the ASTH CTG have been busy with many studies of new anticoagulant agents in prophylaxis and treatment. ITP seems to be attracting industry sponsored research with 2 thrombopoeitin agonists in phase II studies and Roche keen to support a study of rituximab in refractory ITP.

Unfortunately no formal ASTH CTG meeting occurred in the last 12 months. Nevertheless the ASTH CTG is always keen to receive new members and new ideas.

Interested people or any enquiries may be directed to:

Tim Brighton (*t.brighton@unsw.edu.au*) or
Douglas Coghlan (*douglas.coghlan@flinders.edu.au*).

Tim Brighton

NEW AND EMERGING TECHNOLOGIES GROUP REPORT

The main event in 2006 for the NET group was the 2nd ASTH Scientific Workshop held on the 14th October 2006 at the Centre for the Arts in Hobart, the day before the HAA conference. It was another successful event with 88 delegates attending three sessions: 1) Reviews, 2) New Technologies and 3) Case Studies.

Delegates were fortunate to hear presentations from many eminent local speakers from Australia and New Zealand, plus one of the invited international speakers to the HAA conference, Dr Kandice Kottke-Marchant, the President elect for the International Society of Laboratory Haematology. Dr Kottke-Marchant provided an overview of the laboratory investigation of platelets and a number of interesting case studies related to platelet disorders. Thank you to all presenters and delegates for attending. A more in-depth report on the Workshop is provided elsewhere in this newsletter by Susan Rodgers.

The organisers, ASTH and NET group would like to acknowledge and thank the following sponsors of the 2006 Hobart Workshop: Bayer Healthcare, In Vitro Technologies, Medtel-Haemoscope, Diamed, Helena Laboratories, International Society of Laboratory Haematology, Dade-Behring and Roche Diagnostics.

Based on the success of the Melbourne (2004) and Hobart Workshops, preliminary planning is already underway for a similar event prior to the 2007 HAA in Brisbane. An initial call for presentations from NET group and ASTH members will occur in early 2007.

Murray Adams

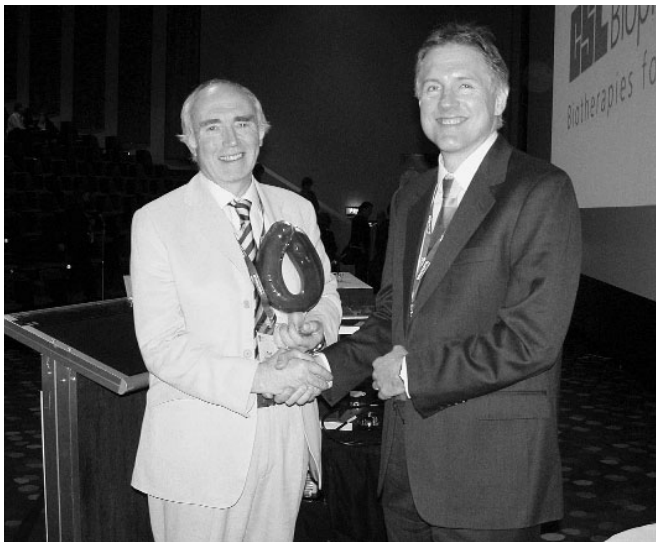
THE 2006 BARRY FIRKIN ORATION

Attendees at the Hobart ASM had the opportunity to hear some excellent presentations. This report summarises the Firkin Oration delivered by Professor Ted Tuddenham, who brought to the meeting the benefit of his extensive work in coagulation science.

For 18 years he was the head of he MRC Thrombosis and Haemostasis Research Unit at Imperial College's Hammersmith Hospital campus. Earlier this year he moved from full time basic science research to become the Clinical Director of the Haemophilia Centre at the Royal Free Hospital in London.

Professor Tuddenham gave this year's lecture on the history of factor VIII. He began the story by citing reference to a male bleeding disorder in the rabbinical writings of the second century. Descriptions even as recent as Queen Victoria's family experience with haemophilia do not allow distinction between haemophilia A or B.

Specific protein deficiency was first postulated by Addis in Edinburgh in 1910, and 20 years later Patek and Taylor and later Minot and colleagues in America led attempts to purify factor VIII, referred to as antihemophilic globulin (AHG), found in the euglobulin fraction. As late as 1952 cross correction studies between different patients with X-linked haemophilia differentiated Haemophilia A from the rarer Haemophilia B. This characterisation allowed development of methods for purifying the correcting factor.



2006 Barry Firkin Orator Ted Tuddenham with Mark Smith

In 1960 a committee of the precursor of the ISTH decided on Roman numerals to designate clotting factors and AHG was assigned factor VIII. Judith Pool soon discovered that cryoprecipitation concentrated most of the factor VIII in plasma in a closed bag with simple apparatus in a blood bank, heralding the modern era of haemophilia care. Professor Tuddenham showed a classic old photo of a young man by his bed at home, his infusion equipment sitting on top of his bedside freezer storing cryoprecipitate for home treatment of a bleed. Low purity cryo saved many lives in the early years of haemophilia treatment.

continued on page 4

THE 2006 BARRY FIRKIN ORATION

continued from page 3

The plasma fractionation industry developed out of world war II methods for making albumin and other fractions (Cohn fractionation) for use in the theatre of battle. Multiple donor pools in the 1970s produced purer and higher potency factor VIII preparations that could be freeze dried and stored. Excitement over small volume, effective infusion therapy was devastatingly countered by the notorious transmission of HIV and HCV to most haemophiliacs in the developed world. Isolation of factor VIII for biochemical characterisation was hampered by copurification with another factor, first identified by Zimmerman as Factor VIII related antigen in 1976.

With the advent of monoclonal antibodies for protein purification and the development of genetic engineering techniques for in vitro synthesis of such proteins the stage was now set for a race to clone factor VIII and make synthetic factor for treating patients. Tuddenham's group acheived completely pure factor VIII by 1982 and collaborated with Genentech on the cloning in 1984, simultaneously with a similar result from Fass working with Genetics institute. Synthetic factor VIII had become the standard treatment for haemophilia by 1990.

Tuddenham completed the story by making reference to the significant modern day issues in haemophilia management: inhibitory antibody formation causing clinical resistance to FVIII treatment; most of the worlds haemophiliacs in developing economies cannot afford FVIII concetrates of any kind; and finally, the challenge of gene therapy to potentially cure haemophilia.

The only area not presented in depth was the impact of molecular technology in helping to avoid vertical transmittance of haemophilia. A story like this, covering two millennia, delivered by a key character in that compelling saga, was indeed a treat to behold.

Mark Smith

UPCOMING MEETINGS IN 2007

MEETING	WHERE/DATES	CONTACT
The 2nd International Symposium on Women's Health Issues in Thrombosis and Haemostasis	Vienna 2-4 February 2007	*www.palexconventions.co.il*
47th British Society of Haematology ASM	Bournemouth 30 April - 2 May 2007	*www.b-s-h.org.uk*
XXth International Symposium on Technological Innovations in Laboratory Haematology	Miami 8 - 11 May 2007	*www.islh.org*
XXIth Congress of the International Society on Thrombosis and Haemostasis	Geneva 6-12 July 2007	*www.isth2007.com*
South Pacific Congress (New Zealand Institute of Medical Laboratory Science (Inc), Australian Institute of Medical Science & New Zealand Cytology Society)	Auckland 21 - 24 August 2007	*www.aims.org.au*
British Society for Haemostasis and Thrombosis Annual Meeting	Bath 26 - 28 September 2007	*www.bsht.bham.ac.uk*
ASTH Scientific Workshop	Gold Coast 13 October 2007	*m.adams@curtin.edu.au* *emma_perrin@health.qld.gov.au*
HAA2007 **9th HSANZ/ANZBT/ASTH Annual Scientific Meeting**	Gold Coast 14 - 17 October 2007	*www.fcconventions.com.au/HAA2007* Abstract submission closes July 2007
4th International Conference on Thrombosis and Hemostasis Issues in Cancer	Bergamo, Italy 26 - 28 October 2007	*info@bergamoconference.com*
The American Society of Haematology 49th Annual Meeting	Atlanta 8 - 11 December 2007	*www.hematology.org*

4TH ASIAN-PACIFIC CONGRESS ON HAEMOSTASIS AND THROMBOSIS SEPTEMBER 21-21, SUZHOU, CHINA

Hatem Salem

The 4th Asian-Pacific Congress on Thrombosis and Haemostasis was Held in Suzhou, China in September of this year. I was lucky to be able to attend this event. I was pleased to note that the Australasian representation was prominent at this meeting. We had a significant number of speakers and other delegates. This was in contrast to previous meetings where we were poorly represented.

The meeting was highly successful in achieving its aims. It brought together over 600 scientists and clincians to discuss recent advances in hemostasis and thrombosis. It also showcased the high quality research activity in different laboratories in South East Asia. In addition to 220 abstracts, the meeting highlights including several symposia and plenary lectures. The International Society of Thrombosis and Haemostasis hosted a full educational day which was very informative and extremely well received. The scientific committee did achieve its aim of delivering a high quality program that has brought all delegates up to date in their field of interest.

Koji Suzuki from Mie University Graduate School of Medicine in Japan presented a wonderful plenary on protein C inhibitor. Koji was the first person to purify and characterise this protein over 20 years. He highlighted the multifunctional roles of this serpin in thrombosis and haemostasis. This protein while initially thought of as a protein C inhibitor was subsequently noted to be a potent inhibitor of the thrombin thrombomodulin complex and urinary plasminogen activator. It is present in plasma and also in large quantities in seminal fluid. It appears to play a role in the regulation of fertilisation, thrombosis and fibrinolysis. In his talk, Koji highlighted the link between fibrinolysis and cancer spread. Using renal cell carcinoma as model, PCI appears to play a critical role in regulating the metastatic potential of this tumour by interfering with both the detachment of cancer cells and also their ability to establish new blood vessels (anti-angiogenic role). I learnt a lot from this presentation particularly the increasing complexity of the role of serpins in multiple patho-physiological events.

There were several other penuries, notably a very elegant presentation from our own Beng Chong on drug induced thrombocytopenia. Ben focussed his discussion on the important role of Glycoprotein Ib-IX as a drug-related auto-antigen. His presentation was very well received by all.

Ross Baker introduced us to the Haemophilia Registry and highlighted the role that registries play in improving patient care. This was a very timely presentation given the significant health care changes that many South East Asian countries are experiencing. Personally I was very impressed by the large number of patients with serious bleeding in many of the Asian countries. The care of these patients particularly the large number of severe haemophiliacs is a challenge that these countries currently face. It is somewhat reminiscent of the problems that our patients experienced 20-30 years ago, before the wide availability for replacement products.

I was very impressed by many presentations on molecular aspects of coagulation and platelets. Clearly there are several laboratories in many Asian countries other than Korea and Japan that are very well equipped and carrying out state of the art studies. Equally impressive was the large number of traditional medicines that have for centuries been known for their activity as antithrombotics. Many of these are now undergoing careful and thorough scientific evaluation for their potential using complex biochemical and molecular techniques. Interestingly some of these medications have the combined effect as inhibitor of platelet activation but can also have potent anti-hypertensive effects. This combination places these agents in a strong position as potential anti-atherosclerotic agents.

In addition to a strong scientific program, the social aspects of the meeting were a highlight. The presidential dinner was a great party that all enjoyed. The hospitality of our Chinese colleagues was phenomenal.

At the council meeting that both Michael Berndt and I attended we discussed ways by which the study and practice of thrombosis and haemostasis can be improved in the region. The need for countries to learn from each other and the important roles of more advanced countries such as Japan, Korea and Australia was stressed.

We discussed the desirability of establishing exchange programs and foster the learning of young talents. The Japanese Society of Haemostasis and Thrombosis offers travelling scholarship to young scientists from South East Asia to attend the annual Japanese meeting. This program has been very well received and has resulted in a significant number of applications by young scientists. This international exchange has very many positive effects and can result in mutually beneficial outcomes. The ASTH should look carefully at this model and consider a program that may help us identify future leaders in the field from within Asian countries.

The APCTH meeting was relatively small compared to the large ISTH meeting. This medium size event has considerable advantages as it allows more opportunities for discussion and closer interactions that could lead to future research and collegiate opportunities. This is an important feature of this conference. Both Michael Berndt and I were sufficiently impressed that we felt we should host this meeting in Australia. We made out intentions clear to the APSTH council. Hopefully we will get the chance to host the meeting in 2010 or 2012.

The next APSTH Congress is in two years. It will be in Singapore. Our colleagues over there are working on an exciting and stimulating program. I encourage all ASTH members to consider attending the meeting. It will be a great opportunity for all to appreciate what is going on in South East Asia. I also encourage all ASTH members to join the APSTH. Membership is free (at least for the time being). From my observations, I have little doubt that a strong APSTH will serve us all very well, and it is in our interest to join in building this strong group rather that stand and watch from a distance.

HAA HOBART

First congratulations to the organising committee for putting together an interesting scientific and educational programme. Some of the highlights of a meeting of this size include the ability to catch up with local colleagues but also to be able to meet and talk with the invited international speakers.

Two entertaining sessions from my perspective were a customary discussion on new anticoagulants and a session of snake bite coagulopathy and their management.

Drs Chris Ward – did I mention he was from Sydney – and Alex Gallus – not from Sydney, engaged in a lively debate about the merits and disadvantages of new anticoagulants using as a context the greatest movie ever made – "Monty Python and the Holy Grail."

Drs Isbister and Brown presented case histories on snake bites and their subsequent data analysis. The data suggest that current treatment protocols should use less antivenom doses and highlighted the self limiting nature of the venom induced systemic fibrinolysis. For my fellow New Zealanders the best first aid for snake bites in Australia is lie still and ring the ambulance on your mobile! If you can get a look at the snake that bit you that might also be helpful.

Prof David Wilcox provided some insight into the future of gene therapy using a novel platelet granule based delivery model for factor VIII. The preliminary laboratory models demonstrate the successful incorporation of the factor VIII gene and subsequent production and storage of factor VIII within mouse platelet alpha granules resulting in reduced blood loss in animal models.

Dr Saskia Middledorp from the Academic Medical Center in Amsterdam and Dr Claire McLintock – also not from Sydney – reminded us of limited and poor evidence to support antepartum thrombo-prophlaxis to prevent adverse pregnancy outcomes in women with thrombo-philia. Fortunately a number of clinical trails are currently underway and should be available within the next few years.

I look forward to the warmer climes of the Gold Coast in 2007.

Sunjeev Chunilal

Claire McLintock, Saskia Middledorp and Sunjeev Chunilal, Hobart ASM

ASTH WORKSHOP, HOBART, OCTOBER 2006

It has been a few years since I attended an ASTH workshop, and found it to be an interesting day, both for the presentations and the opportunity to speak to other people during the breaks. About 90 people attended the workshop held at the Dechaineux Theatre in the Centre for the Arts of the University of Tasmania. It is an interesting building, originally the IXL Jam Factory, built on land reclaimed from the Derwent River by the convicts. Original wooden beams and other features were retained in the renovations, which won an architectural prize.

Emmanuel Favaloro, from Westmead Hospital, was the first speaker, with a review of the current status of VWD. This complex area seems to be becoming more straight-forward with recent information. I was pleased to hear that there are no major changes in the revised classification published this year. One change is clarification of the classification of VWD Vicenza as type 1. Emmanuel spoke later about the identification of auto-antibodies to VWF. For this purpose, it seems that the collagen binding assay may be more successful than the ristocetin cofactor assay, but identification of antibodies is still difficult.

Joanne Joseph, from St Vincent's Hospital, gave an interesting presentation about the use of flow cytometry for the assessment of platelet function and activation. The ability to analyse results on small volumes of blood (with either normal or reduced platelet counts) and to also detect platelet activation make this a useful technique which will become more widely used in the future.

Other tests useful for detection of hypercoagulable states were the subject of two other talks. Jenny Curnow from the Royal North Shore Hospital discussed the relative merits of the endogenous thrombin potential (ETP) and overall haemostatic potential (OHP). The ETP was measured using the commercial calibrated automated thrombogram (CAT) or thrombinoscope developed by Hemker, and determines the amount of thrombin generated. The OHP uses fibrin as an end-point, and is a measure of the clotting pathway as well as fibrinolysis. The ETP was not affected by pregnancy, while the OHP was increased and also showed a decreased fibrinolytic potential. Their conclusions were that both tests are useful, each providing different haemostatic information. The commercial CAT is well-standardised and simple, but expensive, while the OHP is simple and cheap. Ray Dauer from the Austin Hospital used the ETP-Dade-Behring kit, and a range of other hypercoagulable markers to determine that seal oil may be more beneficial than fish oil for lowering CVD risk factors in blood.

There were also several presentations on warfarin monitoring, which included discussion of near-patient testing, as well as an internet-based program for monitoring. A variety of other topics were also covered during the day. The last session was presented by Kandice Kottke-Marchant of the Cleveland Clinic Foundation in the USA. She presented case studies of platelet function disorders which involved both clinical and laboratory features. Congratulations to Emma and Murray for organising such a varied and interesting program.

Susan Rodgers

AIMS/AACB 2006 NATIONAL MEETING

The conference was held in Hobart at the Hotel Grand Chancellor, which provided excellent facilities and was well located for the delegates to enjoy the tourist attractions in and around Hobart. There were over 700 delegates who were treated to an excellent scientific and social program and trade display. The conference commenced with a day devoted to the RCPA QA program updates which included presentations on the routine and specialised haemostasis programs. The Scientific program had many concurrent sessions covering Biochemistry, Haematology, Blood transfusion, Microbiology and Histology. As the program was so diverse there was only a small component for haemostasis, and these were of a more practical nature. Presentations included coagulation analyser selection and operational issues, factor VIII assay methods, identification of factor inhibitors, heparin sensitivity of APTT reagents, lupus anticoagulant testing, rapid preanalytical processing of coagulation samples, point of care testing for oral anticoagulant therapy monitoring, and laboratory diagnosis of von Willebrands disease. The abstracts from the meeting may be reviewed in the Australian Journal of Medical Science, Vol 27, No 4, November 2006.

Michael Wheeler

ASTH WINNING ABSTRACT:

ANALYSIS OF THE SENSITIVITY OF THE OVERALL HAEMOSTATIC POTENTIAL (OHP) ASSAY TO COMPONENTS OF THE COAGULATION SYSTEM

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[2]Department of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, NSW

Aim:

To determine the sensitivity of the OHP assay parameters to changes in components of the coagulation system. To assess changes seen with a modified OHP using tissue factor as the coagulation trigger.

Methods:

In the standard OHP we use a small amount of thrombin to trigger fibrin generation in platelet poor plasma (PPP) with rt-PA added to initiate fibrinolysis. In order to model *in vivo* events more closely, we developed a modified version of the assay using tissue factor (TF) as the coagulation trigger. We then analysed changes seen in assay parameters after spiking PPP, to alter levels of components of the coagulation system including: antithrombin, fibrinogen, prothrombin and factors V, VII, VIII and X. Results were compared with reference intervals we have established in a healthy Australian population. Method comparisons were analysed using a repeated measures ANOVA.

Results:

Fibrinogen levels (0 to 10g/L) showed a direct correlation with all OHP parameters: OCP (overall coagulation potential), OHP, OFP (overall fibrinolysis potential), maximum OD (Max OD), maximum slope of the OCP curve (Max slope) and delay in onset of fibrin generation. Factors II, VIII and X showed similar correlations for fibrin generation parameters but fibrinolysis was not altered until the individual factor levels were <= 5% and therefore clot formation was markedly reduced. Samples from individuals with elevated FVIII levels were associated with increased fibrin generation and reduced fibrinolysis. Lowering of the high FVIII levels reduced fibrin generation into the normal range but fibrinolysis remained reduced in these hypercoagulable individuals. Standard OHP assay parameters were not influenced by factor V and VII until levels were <=5%, however the TF triggered assay showed correlation for all assay parameters with FV and FVII levels. Reduced antithrombin levels showed more rapid fibrin generation, consistent with a hypercoagulable state.

Conclusions:

We have shown that the OHP is influenced by various components of the coagulation system with both hypo-coagulable and hypercoagulable states demonstrated. Fibrin generation and fibrinolysis parameters show different responses to alterations in coagulation factor levels. The modified OHP, triggered by TF, may be more sensitive than the standard assay to abnormalities of Factor V and VII.

Mark Smith with 2006 ASTH medal winner Jennifer Curnow

ASTH TRAVEL GRANT WINNERS 2006

(each winner received $1000)

Vanessa Cole for the molecular characterisation of a protein S deficient pedigree

Ashley Ng for a review of TTP at the Royal Melbourne Hospital

Lay Tay for a comparative study of different methods for monitoring LMWH