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

Welcome to the August issue of the newsletter and it's a big one with lots of news and information. Included are the following:

- Hobart HAA ASM 2006 Update
- Presidents report
- Secretariat news
- New and Emerging Technologies Report: Scientific Workshop Hobart
- Clinical Trials Group Report
- Report on International Society of Laboratory Haematology, Amsterdam
- Report on Annual Meeting of SSC of ISTH, Oslo
- Obituary Joe Margolis
- Upcoming Meetings

Thank you to those members who contributed to this edition.

See you in Hobart.

Emma Perrin

COME TO THE ANNUAL SCIENTIFIC MEETING IN HOBART

OCTOBER 15-18

The 2006 Barry Firkin Oration on the Education Day Sunday will be given by Ted Tuddenham, Director of the Haemophilia Centre at the Royal Free Hospital in London. His oration, entitled "The FVIII Story" should prove to be a fascinating insight into his research as head of the team that purified the FVIII gene. To encapsulate the areas covered by this oration I will cite Ted Tuddenham's own words when he replied to the invitation: "That title is fine with me as it encapsulates what I hope to do in the lecture, which is to tell an interesting story about the history of a molecule. I am in print in various articles and chapters on the subject, which some may have read, but I will use additional material and bring the story up to date." Later in the meeting he will discuss Tissue Factor and Vitamin K epoxide reductase.

The HAA enjoys a reputation for providing a strong scientific and clinical focus as well as an occasion to allow friends and colleagues from the Haematology field to catch-up and relax – take some time to ask Ted Tuddenham about his other passions, mycology and bodging!

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ASTH COUNCIL 2005-2007

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COME TO THE ANNUAL SCIENTIFIC MEETING IN HOBART

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The program this year includes several international and local speakers who will be presenting some exciting topics such as new diagnostic technologies with Dietmar Fries (Austria) on TEG-POC monitoring for detection of hyper-fibrinolysis and therapy, Kandice Kottke-Marchant (USA) on laboratory testing and clinical implications of aspirin and clopidogrel resistance, pre-implantation genetic diagnosis for Haemophilia (Peter George) and Chris Ward on thrombin generation tests.

Our invited international speakers also include Saskia Middeldorp, Associate Professor of Vascular Medicine at the University of Amsterdam. Her research interests include thrombophilias and anticoagulant therapy for obstetric complications. Her main focus for the meeting will be obstetric issues in thrombosis with sessions on fetal loss and thrombophilias and VTE in pregnancy. In addition, she will take a Masterclass and wants her Masterclass to provide an opportunity for clinicians to discuss their difficult clinical clotting problems. She would like to receive details of any of your difficult cases beforehand so she can review the relevant literature to discuss in the Masterclass. So, if you have a case you'd like to discuss, please could you email the details to Claire McLintock by September 15th (*claire.mclintock@dml.co.nz*) and she will forward them to Saskia. We promised we'd give her a month to do the research and think it's a great opportunity that should provoke stimulating discussion.

Our final invited international speaker is Dr David Wilcox, Associate Professor of Pediatrics at the Medical College of Wisconsin. We are particularly looking forward to his lectures on the topic of gene therapy in the field of bleeding disorders with a Masterclass on the same topic to allow more informal discussion.

Add a wealth of local talent, some imported, some home-grown and we promise vigorous debates on the new anticoagulants, enthralling basic science – we'll wow you with thrombin generation, plasminogen activators, fibrinogen, obstetrics and the antiphospholipid syndrome. And in a final flourish our last session is on Snake Envemonation – one to get your teeth into!

Key information.

- Earlybird Registration closes 18th August.
- ASTH Scientific Award – $2000 and the ASTH Medal awarded to the most outstanding abstract submitted by a young clinical or laboratory researcher.
- ASTH travel grants available
- Don't forget to also register for the ASTH Scientific Workshop Saturday Oct 14 (see NET Report in this issue)
- For all ASM details see conference website: *www.cdesign.com.au/haa*2006

Claire McClintock and Ali Bianchi

FROM THE PRESIDENT

The clinical front of coagulation has for many years been strongly influenced by concerns over safety and cost of treatments. Plasma derived therapeutic products continue to attract significant attention. There are several current examples. At the end of July, the Queensland Health Blood Management Programme convened a one-day meeting on Immunoglobulins, focusing on safety, supply and clinical indications. This important initiative, brought together clinicians, ARCBS, commercial fractionators and local government representatives, and promoted informed opinion on issues of use indicators and risk. Furthermore, Australia's National Blood Authority recently concluded a tender process for procurement of therapeutic products for haemophilia treatment, effectively expanding treatment options, and improving security of supply, for patients with haemophilia: (see *http://www.nba.gov.au*/PDF/FACT%20SHEET%20-%2018%20M*ay*%202006%20-%20D*efined*%20B*lood*%20P*roducts.pdf*)

The Australian Government has committed to undertake a review of its arrangements for the supply of plasma fractionation services for plasma collected in Australia. This project is highly relevant to the Australia-United States Free Trade Agreement, and it should be reported to the Minister of Health and Ageing in January 2007. The review committee is consulting widely across Australia and internationally, examining the many possible arrangements for supplying products fractionated from plasma collected by the ARCBS to meet Australian demand for these products. Consistent with free trade agreements, the review will examine the feasibility of procuring plasma fractionation services through open tender processes: (see *http://www.health.gov.au/internet/wcms/publishing.nsf/content/plasma-fractionation-review.htm*). These interesting events demonstrate the political relevance and importance of clinical coagulation medicine.

The society is actively pursuing building a new ASTH web site. While the current web site has served us well in the past, it clearly no longer meets the needs of our membership. Council has commissioned the services of the web site design group "DDSN Interactive" to build a modern site closely focused on the core activity of the Society. It has been frustrating to the council that we have fallen behind expectations in terms of an informative and interactive web site. Members who have a specific interest in this should make themselves known to our Project Officer Megan Sarson-Lawrence, who will inform you when the new site is available for testing and feedback. This "road testing" should take place later in August, and shortly thereafter give us an internet profile that will work well for the Society and its members.

Mark Smith

SECRETARIAT NEWS

The 2006-07 membership renewals were sent out in early July- thanks to those who have returned them so promptly. Several members have queried why they were being asked to pay their membership fees so soon after just paying the previous years fees. By way of explanation, the ASTH membership year runs parallel to the Australian financial year and as such new membership fees become due on the 1st July. Unfortunately, there was no one in the ASTH Secretariat position this time last year and as a result the 2005-06 membership notices were not sent out until early in January.

At its last teleconference, Council agreed to introduce a new membership category, that of Emeritus Member. This category is open to previous members who have contributed to the field of haemostasis and thrombosis and have now retired. Emeritus membership has no fee and eligible members will be sent a copy of the ASTH newsletter free of charge. If you would like to renew your membership using this new category please let me know.

DDSN have been engaged to re-develop the ASTH web site. Take a look at their site at *www.ddsn.com* and check out the links to other sites they've developed to see what the new ASTH site might look like! If you have any suggestions as to what material should be included on the new site please let me know. We're already looking at the possibility of on line membership payments and a member database to help you locate other members who share similar interests or work in specific areas. If everything goes to plan the new site should be launched before the end of August.

The plans for the ASTH Scientific Workshop and ASM are also progressing well. A brochure for the ASM was mailed out to all members recently with early bird registration ending on 18th August. Registration for the ASTH Workshop should be available through the ASM web site at *www.cdesign.com.au/haa*2006/ but if you have any difficulties or further queries please contact me. A workshop registration form will also be available on the new ASTH web site when it is launched. I encourage you to register early and look forward to meeting many of you there.

Finally for this edition, I'd like to welcome (in alphabetical order) CSL Bioplasma, Novo Nordisk and Wyeth as ASTH corporate sponsors.

Megan Sarson-Lawrence

UPCOMING MEETINGS

MEETING	WHERE/DATES	CONTACT
XXXI World Congress of the International Society of Hematology (ISH)	San Juan, Puerto Rico 9-12 August 2006	*www.ish*2006.*org*
18th International Society of Fibrinolysis and Proteolysis Congress	San Diego 27-31 August 2006	*www.med.unc.edu/isth*
4th Asian-Pacific Congress on Thrombosis and Hemostasis	Suzhou, China 21-23 September 2006	*www.apcth.org.cn*
British Society for Haemostasis and Thrombosis Annual Meeting	St Helier, Jersey 4-6 October 2006	*www.bsht.bham.ac.uk*
ASTH Scientific Workshop	Hobart 14 October 2006	*m.adams@curtin.edu.au* *emma_perrin@health.qld.gov.au*
8th HAA Annual Scientific Meeting	Hobart 15-18 October 2006	*www.cdesign.com.au*/HAA2006
AIMS National ASM	Hobart 23-27 October 2006	*www.aims.org.au*
The American Society of Haematology 48th Annual Meeting	Orlando, Florida 9-12 December 2006	*www.hematology.org*
XXI ISTH Congress	Geneva, Switzerland 6-12 July 2007	*www.isth*2007.*com*
ASTH Scientific Workshop	Gold Coast 13 October 2007	*m.adams@curtin.edu.au* *emma_perrin@health.qld.gov.au*
9th HAA Annual Scientific Meeting	Gold Coast 14-17 October 2007	*emma_perrin@health.qld.gov.au*

NEW AND EMERGING TECHNOLOGIES GROUP REPORT

It has been a busy few months since the last report, with a substantial amount of effort dedicated to organising the major event of 2006, the ASTH Hobart Scientific Workshop. This will be held the day before the 8th Joint Scientific Meeting of the HSANZ, ANZSBT and ASTH on Saturday 14th October at The Dechaineux Theatre, Centre for the Arts, Hobart.

The provisional program of topics and speakers, registration form and tax invoice, which have recently been distributed to ASTH members, are available from Megan Sarson-Lawrence at the ASTH office (*asth@bigpond.com.au*) and will soon be available from the HAA Conference website (*http://www.cdesign.com.au/haa*2006/). Please note that the Workshop registration fee for non-members of the ASTH is more expensive than the combined ASTH membership fee and ASTH member Workshop registration fee. If you are not a member of the ASTH, then it is worth joining the ASTH as member if you are attending the Workshop.

As well as local speakers, the Workshop will also include several case study presentations from Dr Kandice Kottke-Marchant (see insert) from the Cleveland Clinic Foundation in Ohio, USA, who is one of the invited international speakers for the HAA meeting held 15th-18th October. There is still flexibility in the program for further case study presentations. If anyone is interested please contact Murray Adams (details below).

I would like to acknowledge the following for their kind sponsorship of the Workshop; Bayer Healthcare, In Vitro Technologies, Medtel – Haemoscope, Diamed, Helena Laboratories and the International Society of Laboratory Haematology. I would also like to thank the following individuals for their input, advice and help in organising the Workshop; Emma Perrin, Megan Sarson-Lawrence, Katherine Marsden, Emmanuel Favaloro, Janet Crack at the University of Tasmania, ASTH Council and Meredith Wilson and Penny Archer at Conference Design, as well as the presenters who have enthusiastically agreed to contribute to the success of the day.

For further information or queries about the ASTH Hobart Scientific Workshop please contact Megan Sarson-Lawrence [(+61 3) 9388 8711, *asth@bigpond.com.au*], Murray Adams [(+61 8) 9266 4316, M.A*dams@curtin.edu.au*] or Emma Perrin [(+61 7) 3240 2053, E*mma_Perrin@health.qld.gov.au*].

Murray Adams

Dr Kandice Kottke-Marchant

Section Head of Hemostasis and Thrombosis in the Department of Clinical Pathology at the Cleveland Clinic Foundation, Cleveland, Ohio, USA

Dr. Kandice Kottke-Marchant is currently Section Head of Hemostasis and Thrombosis in the Dept. of Clinical Pathology at the Cleveland Clinic Foundation, in Cleveland, Ohio, one of the leading cardiovascular hospitals in the United States. She is the President-Elect of the International Society for Laboratory Hematology (ISLH) and member of the Area Committee for Hematology of CLSI. She received her MD and PhD from Case Western Reserve University in Cleveland, OH. Her research interests are aspirin and clopidogrel resistance and nanomimetic tissue engineering of vascular graft prostheses.

ASTH TRIALS GROUP

The ASPIRE 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 ~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 is being submitted to University of Sydney and will be distributed to interested sites soon. We have reached the interview stage 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 one week ago. Comments and responses to participate in the pilot study are eagerly awaited.

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

INTERNATIONAL SOCIETY FOR LABORATORY HAEMATOLOGY (ISLH)

AMSTERDAM – 25-28 APRIL 2006

Roslyn Bonar

The XIXth International Symposium on Technical Innovations in Laboratory Haematology was held in the NH Grand Hotel Krasnapolsky located centrally in Dam Square, Amsterdam, amid a vast network of canals. Although the weather was a little brisk at times, it was only a short walk to a varied choice of cafes and restaurants that catered to every style and flavour. Due to the impending Queen's Birthday weekend there were many activities and sights to explore, from Carnivals at your door to bands playing in the streets.

The meeting was very well attended with around 800 registrants. The sessions opened on Tuesday at lunchtime, giving us a little time to recover from our jetlag. The current report lists some of the highlights from a personal perspective.

Dr Machin presented an informative talk on the 'Continuing developments with the platelet count'. Changing methods from impedance to multiple light scatter and/or fluorescence improves the ability of automated analysers to count platelets. The inaccuracy of the low platelet count (usually being overestimated), results in undertransfusion of platelets. It was suggested that optical platelet counting may be superior to impedance counts.

Dr Philip de Groot provided us with some new insights into diagnostic tests for Antiphospholipid Syndrome. Lupus anticoagulant (LAC) can be caused by anti-β2GPI antibodies or anti-prothrombin antibodies. Studies reported that a β2GP1-dependent LAC, but not a prothrombin dependent LAC, correlates better with thromboembolic complications.

Piet Meijer from ECAT presented a short overview on the performance of FVIII inhibitor assays in clinical laboratories. Essentially, results illustrated lower between laboratory variation with the Nijmegen assay compared to the Bethesda assay. This was of special interest because a recent RCPA QAP exercise also showed there is need for improvement in the measurement of FVIII inhibitors.

Carl-Erik Dempfle presented 'Pitfalls in the use and standardization of D-Dimer testing.'

As we all know the standardisation of the D-Dimer assay presents a very perplexing problem. A possible solution may be to produce a common calibrator for D-Dimer assays reflecting the composition of cross linked fibrin derivatives found in the clinical plasma samples from a target patient population. This could be used by manufacturers to re-evaluate the cutoff values for different diagnoses. Piet Meijer's group has also recently published a paper on their attempts at D-Dimer harmonisation. The RCPA QAP has also done some work in this area and recently presented a trial at the ISTH meeting in Sydney last year.

Dr John Lloyd gave an interesting presentation on one stage vs two stage FVIII assays for the detection of discrepant haemophilia, which occurs in up to a third of patients with mild haemophilia. He described the difference in assay results for these patients between a one stage and two stage FVIII assays. He also presented studies using 3 commercial FVIII chromogenic assay kits using longer incubation times, in which his IMVS group showed that two of the three were suitable for the identification of these discrepant haemophilia patients.

In the same session, Dr Steve Kitchen from NEQAS UK presented how FVIII:C and other coagulant assay results vary between test centres and how this still presents a major problem. There are several variables that may contribute to this situation, such as brand of deficient plasma and APTT reagent, calibration curves (how often these are set up) and assay design.

The NCCLS guidelines (1997) recommend construction of a working reference curve with each run of assays and at least three dilutions of test plasma. Many modern instruments utilise reference curves stored in memory. Results of NEQAS exercises (as well as RCPA QAP exercises) demonstrate that improvements in FVIII assay results are required.

One area of disappointment for me was that there was only minimal coverage of the POC-INR instruments. This is an area that is rapidly expanding and with the availability of home testing and possibly pharmacy-based testing the need to establish external QA is paramount.

Thursday night was the conference dinner. After a quick dash from the last presentation to the back of the Hotel, we were treated to a one hour leisurely canal cruise. After viewing the wonderful sites and architecture of Amsterdam, we arrived at the Five Flies Restaurant for a delicious four course New Dutch feast. A short walk later brought you back to the Hotel.

The meeting was a very enjoyable and educational experience and I look forward to the next meeting in Miami, Florida, in 2007.

52ND ANNUAL MEETING OF THE SCIENTIFIC AND STANDARDISATION COMMITTEE (SSC) OF THE ISTH

Emmanuel J Favaloro

The 52nd annual Scientific and Standardisation Committee (SSC) meeting of the International Society on Thrombosis and Haemostasis (ISTH) was held in Oslo, Norway, between June 28th and July 1st.

The meeting began with a Symposium on von Willebrand Disease (vWD) – my favourite topic – held in honour of the first publication in 1926 by Erik von Willebrand, where he describes the condition we now know as vWD, but which he called 'hereditar pseudohemofili'. Chaired by Augusto Federici, there were talks by several 'heavies' in the field: Robert Montgomery, Zaverio Ruggeri, David Ginsburg, Evan Sadler, Francesco Rodeghiero, Ian Peake, Dominique Meyer, and Pier Mannucci. Topics included: synthesis, structure and function of vWF; modulation of vWF function by ADAMTS-13; an update on the classification of vWD; epidemiology, clinical aspects and therapeutic management of VWD; clinical, laboratory and molecular markers of VWD. It was a pleasure to hear the talks from such an august collection of individuals.

An educational symposium titled: "Diet, omega-3 fatty acids & atherothrombosis" took up the entire next morning, and was relevant for those with an interest in nutrition related thrombosis risk. The role of diet and omega-3 in haemostasis presents with conflicting data; but, overall the studies confirm that both play a significant role. The biggest problem relates to issues of study control-compliance in diet studies, selection of appropriate controls, complexity of diets so that the contribution of individual nutrients are difficult to assess. Overall, however, there are many points within haemostasis that omega-3's may play a role: eg to dampen platelet activation; to reduce the expression of adhesive molecules (thus reducing potential plaque development); to reduce various markers of inflammation; affect intra-cellular expression of COX-2; reduction of cytokines; dampening of arachidonic acid pathway; reduction in tissue factor expression; reduction in serum triglycerides, PAI-1 and fibrinogen; and elevation of HDL (ie the 'good') cholesterol. Much of the early work originated in Norway, when it was recognised that Eskimos had ~10% of the myocardial infarction rate of the Scandinavian population, and thought to be reflective of the high fish (oil) diet they 'enjoyed'. I particularly enjoyed the talk by deGaetano, who spoke on the benefits of olive-oil (as an Australian of Italian descent, don't I already know this?), the 'French Paradox' (high fat diet but relatively low CHD mortality), and the health benefits of wine consumption (in moderation).

A lunchtime Symposium on platelet function testing was of some interest but the highlight of the day was the afternoon session (Part 1 of the vWF/vWD SSC meeting). There were a series of reports on the recent laboratory test exercise undertaken by the vWF/vWD SSC, and involving 32 participant laboratories worldwide. Our laboratory was the sole Australian laboratory. The exercise was similar to that undertaken in the past by our own RCPA QAP [summarised in [1,2]], in so far as a series (n=8) of plasma samples were distributed for blind testing in assays used in vWD diagnosis, and the return of test results and 'diagnostic interpretations' by participants for analysis by the vWF/vWD SSC. The difference was that this was not a QA exercise. The laboratories involved were all considered 'expert' vWD-testing labs, and test panels used by most of the laboratories were fairly comprehensive. All laboratories (ie 100%) performed VWF:Ag and VWF:RCo. 25 (78.1%) laboratories performed VWF:CB. 18 (56.3%) laboratories performed VWF:multimers. 20 (62.5%) laboratories performed VWF:FVIIIB. 15 laboratories (ie 46.9%) performed all five assays. Six (18.8%) laboratories performed VWF:Ag, VWF:RCo, VWF:CB and VWF:multimers (ie no VWF:FVIIIB). Three (9.4%) laboratories performed VWF:Ag, VWF:RCo and VWF:multimers (ie no VWF:FVIIIB or VWF:CB). One laboratory (3.1%) performed VWF:Ag, VWF:RCo and VWF:CB (ie no VWF:FVIIIB or VWF:multimers). Two (6.3%) laboratories performed VWF:Ag and VWF:RCo (ie no VWF:FVIIIB or VWF:CB or VWF:multimers).

I was pleased to report that the vWF:CB outperformed the vWF:RCo in terms of identifying the loss of high molecular weight (HMW) vWF associated with Types 2A and 2B vWD.[1,2] Type I (/III mixture collagens) performed better than purified Type III collagens.[3,4] However, the vWF:RCo was better at identifying the Type 2M vWD sample. Overall, efficacy of performance of vWF:CB was collagen-source related, whereas performance of vWF:RCo was more random-event related (high variability) plus related to poor sensitivity at low levels of vWF. Other speakers provided information about other aspects of the study (eg vWF:Ag, vWF:RCo, multimers, statistics, diagnosis). The data is planned to be published in the Journal of Thrombosis and Haemostasis (JTH) later this year. **I intend to give a talk updating vWF/vWD at both the forthcoming HAA meeting (October 14th at the ASTH Workshop) and the AIMS meeting (also October; possibly a breakfast session?) in Hobart later this year**.

I gave another talk at this session on pre-analytical variables in vWD testing, and highlighted the issue of cold-

transport/storage of whole citrate blood related problems. Later speakers at this session included: Evan Sadler, who spoke on the updated vWD classification scheme (as well, a vote was undertaken in favour to publish this update in JTH); Anne Goodeve, Lysiane Hilbert and David Lillicrap, who spoke on vWF molecular biology and expression studies; Zaverio Ruggeri and Armin Reininger, who spoke on laboratory assays dependent on shear stress – perhaps the future? There was also a talk on the use of vWF propeptide as a marker of vWF survival in certain vWD subtypes.

The next day began with Part 2 of the vWF/vWD SSC meeting, with most of the session devoted to ADAMTS13 and TTP. Several speakers presented data on this topic. I'm sure that some of the data was the same as that presented last year in Sydney. The FRETS-VWF73 assay seems among the most promising. It's now available commercially, but is very expensive and requires a fluorescence plate reader.

Lunch was a 'committee meeting', comprising representatives from an international collection of haemostasis related external QAPs. I was representing our RCPA QAP (haemostasis) at this meeting. The hope is to develop some consensus towards 'world best practice' as well as to possibly conduct some international QA exercises that would be unlikely to be done internally. As an example, this group hopes to get together to run an exercise for vWD Type 2N. In our geographic region, there are only a few labs (?2-4) doing the test (vWF:FVIII binding assay), so it is unlikely that the RCPA QAP can conduct a meaningful test exercise on its own; however, the exercise would be quite valuable as a broad international exercise.

For me, the afternoon was the factor VIII and IX session, to hear about detection of factor inhibitors. NIBSC has been recently involved in attempting to generate a FVIII inhibitor standard. Again, there is wide scatter of data even among the experts. The RCPA QAP recently conducted an exercise in inhibitor identification in 2005 that has recently been published.[5]

See you in Hobart in October (at the ASTH Workshop and/or the AIMS meeting).

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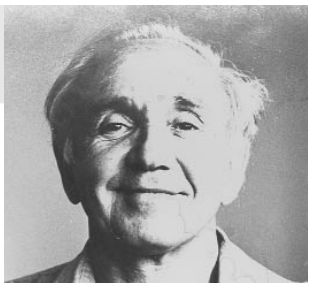
Editors Note: *Due to length restrictions for the newsletter I could not include the whole of Emmanuel's report. When the new ASTH website is operational I promise to include a copy of the full report.*

OBITUARY FOR JOEL MARGOLIS
02.07.1920 – 02.04.2006



Joel was born in Bialystock, Poland, but grew up in Vilna (then Polish but now the capital of Lithuania). He and his family left Poland in 1939, driving North in a truck using solvents from their tannery as fuel. They took a plane to Sweden which was the last out of Poland – the next one crashed. After traveling to England they boarded a ship to Melbourne, where the family set up a tannery making boots for the war effort. Whilst working in the company, Joel read physiology and other medical textbooks in his spare time. He went for an interview at the University of Melbourne and was accepted on the spot to do medicine. It was a great relief to him to get out of the boredom of the tannery, where someone had once asked him "do they have their own language in Poland, or do they all speak broken English?"

After graduation he did a residency in Perth at the Princess Margaret Hospital then moved to Sydney in 1952 and worked in the Royal Children's Hospital Pathology Department where he developed an interest in blood coagulation. He collaborated with Paul Fantl among others in this field, eventually taking a sabbatical to Oxford to study with Rosemary Bigg's group which was then at the forefront of blood coagulation research. One of his classic papers on the Kaolin Clotting Time, a precursor to the APTT, came from the Radcliff Infirmary in 1958. His main focus appears to have been the contact mechanism and kinin formation. Ultimately he gained a D Phil from Oxford University followed by a D Sc from the University of Melbourne.

Upon returning, Joel resumed work at the Children's Medical Research Foundation in Camperdown with John Harley and Albert Lovric. In blood coagulation, he developed new tests and studied silica and fatty acids as contact activators. He was the first to analyse the kinetics of coagulation mathematically. He identified several cases

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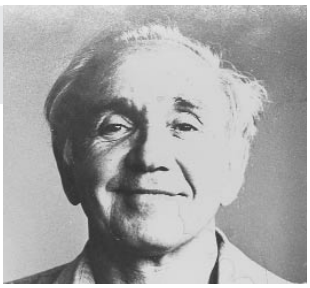
OBITUARY FOR JOEL MARGOLIS
02.07.1920 – 02.04.2006



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of Hageman factor deficiency and confirmed that it did not cause bleeding. For blood analysis, he applied polyacrylamide gel electrophoresis. He used to say proudly that he taught Fred Sanger to run gels – he was greatly amused by this because Fred became a Nobel laureate. He invented a method for sharpening up the many bands obtained by using a gradient in polyacrylamide gel concentration. He published several times in Nature and also invented 2 dimensional gel electrophoresis methods with Ken Kenrick in 1969 (although this is often unfairly attributed to the US team of O'Farrell and Klose who published much later in 1975). These were important methodological inventions which ultimately permitted the development of the new field of proteomics.

Joel thought the gradient gel idea had great potential and founded his own company "Gradient Laboratories", which must have been one of the first biotech companies set up in Australia. He worked from his home in Lane Cove making electrophoresis equipment and gradient polyacrylamide gels in the basement. He also took a part time job at the Red Cross Blood Transfusion Service (RCBTS) in Sydney.

Joel's main project for RCBTS (then headed by Gordon Archer) was to purify factor VIII from cryoprecipitate for treatment of Australia's haemophiliacs. Many of his ideas spun out of this work. Joel developed a gel filtration method using controlled pore glass which was capable of heat sterilisation. This was important at that time when HIV was found to be spreading among haemophiliacs due to use of unscreened donor plasma to make "cryo". To increase factor VIII yield he investigated various stabilizers for preserving that labile molecule in freeze dried form. His method was rapidly adopted by CSL and also later by the New Zealand, Dutch and Canadian Blood Transfusion Laboratories where the product was known as "Margolis factor VIII".

In the course of numerous clotting assays for factor VIII Joel worked out how to handle up to 5 test tubes at a time using a clamp with one hand and a panel of stopwatches with the other. He noticed that when plasma/reagent mixes clotted and were agitated, the kaolin aggregated and the turbid liquid suddenly became clear at the precise endpoint. He patented this idea which had the potential for more accurate clotting tests than were otherwise available at that time. He made a small machine using this principle, in which a small electric motor beat plasma/kaolin mixtures in a row of test tubes with disposable plastic fingers. Chronic shortage of money meant that everything was low cost. The thermostat and pumps were from a fish tank supplier. The plastic fabrication was all done by Joel himself. A full scale multi-channel instrument was developed later at Gradipore. This clotting machine worked really well for factor assays but was not so good for less diluted plasmas in conventional PT and APTT tests. He also developed an "activated deficient plasma substrate" (ADAPS) for more simple factor VIII assays not needing preincubation.

Everyone who ever worked with Margolis agreed that he was a true genius although very difficult to understand at times and with a quirky sense of humour. Among his other innovations was a plastic fraction collector powered by a clock motor where the outlet was moved using 35mm film (with its sprockets). He developed electrophoretic destaining methods and a simple clamp-on preparative electrophoresis device. His colleagues in electrophoresis included Colin Wrigley at CSIRO (who had invented iso-electric focusing) and Keith Williams at Macquarie University. However his last great idea was a large scale preparative electrophoresis apparatus (Gradiflow) which consumed him for the rest of his professional career at Gradipore.

The "Gradiflow" concept was to use move proteins of different size and charge through thin polyacrylamide membranes having different pore size thereby separating a mixture (such as blood plasma) into its various components. Gradipore was financed initially by Perry Manusu, a retired vet with business experience who was impressed with Joel's ideas. Perry and son John were able to raise significant R&D funding for the Gradiflow project so that eventually the company floated on the Sydney stock exchange. They brought in David Solomon, former chief of the polymer science division at CSIRO as a consultant and also Keith Williams from Macquarie University. After Tom Exner joined in 1993, Gradipore diversified into blood coagulation products such as the DRVVT test for lupus inhibitors which provided increasing sales for the company. Gradipore grew rapidly from a small terrace house on Harris Street Ultimo to a much larger ex-CSIRO building at North Ryde and finally in 2002 to a modern marble and glass complex with over 100 employees at Frenchs Forest. However Joel never got to use that ultimate facility and could only wonder about even more recent developments when Gradipore changed its name to Life Therapeutics and moved to Atlanta in the US.

Joel had a stroke in 2000 which handicapped him physically though his intellect remained completely intact. He resided in an aged-care facility at Lane Cove then a nursing home at Petersham until 2006 when he quietly passed away in the company of his children Michelle, Adam and Julian, and brother George. He left his body to the medical school, so his passing was not marked by any funeral.

by Tom Exner, Margo Honeyman and Michelle Margolis