Dear Colleagues,

I am pleased and honored to take over as President of the Canadian Hematology Society from Tom Nevill. Tom is now our Immediate Past President and I want to warmly welcome Aaron Schimmer as our incoming Vice-President. Molly Warner continues as our Secretary and Treasurer and Gail Rock continues as our Executive Vice-President.

On behalf of the entire CHS Executive, it was great to see many of you at the recent CHS Evening at ASH on Sunday December 11, 2011.

I would like to extend a particular thanks to our corporate sponsors, without whose help and support it would not be possible to continue our activities.

Tom has done much to re-energize our organization. In particular, he has served as Editor of “The Microenvironment” and has generously agreed to stay on in this role. Please consider writing an article for our forthcoming issue! This publication reaches many hematologists in Canada and is also read by trainees and other members of our healthcare teams. Tom has also led an initiative to establish a small grants competition entitled the RK Smiley Research Grant program. Again, more information about this will be found in the forthcoming “Microenvironment”.

I think we should all be most proud of the role that each of us plays as members of the CHS in highlighting and encouraging the academic activities and accomplishments of our trainees and junior faculty. At the recent Canadian evening at ASH, a number of trainees and junior faculty and their supervisors and mentors were acknowledged with awards. More on this on pages 3—6 of this issue of “The Microenvironment”.

...continued on Page 2
Canadian Scientific Meetings:
This year, the Canadian Blood and Marrow Transplant Group (CBMTG) led by Dr. Ronan Foley and the Canadian Apheresis Group (CAG) led by Dr. Gail Rock are holding a combined national meeting in Toronto from April 11, 2012 to April 14, 2012. If this is successful, we at the CHS would like to revisit the idea of having a national hematology meeting again.

We also hope to partner with Dr. Catherine Hayward who is hosting the International Society of Laboratory Hematology meeting in 2013. There is an opportunity for Canada to host the International Society of Hematology (ISH) meeting in 2018 as well.

Moving forward, I would like to ask you to consider renewing your membership to our important national organization. Also, please spread the word about the CHS to your colleagues and to trainees. More information about the CHS can be found at our website: www.canadianhematologysociety.org

Sincerely,
Stephen Couban, MD
CHS President

Chers Collèges,


Au nom de tous les membres de l’exécutif, il m’a fait grand plaisir de vous voir si nombreux à la réunion CHS Evening au ASH (Action contre le tabac et pour la santé), le dimanche 11 décembre, 2011. J’aimerai remercier surtout nos sociétés commanditaires de leur soutien, sans lequel il nous serait impossible de continuer nos activités.

Tom a beaucoup fait afin de redynamiser notre organisation. Il a surtout contribué en étant le rédacteur du The Microenvironment (le microenvironnement), et il a généreusement accepté de continuer dans ce rôle. Pensez à la possibilité d’écrire un article pour la prochaine édition ! Cette publication est lue par beaucoup d’hématologues au Canada et elle est lue aussi par les stagiaires et d’autres membres de nos équipes de soins. En plus, Tom dirigent une démarche menant à l’établissement d’une petite concours de subventions, avec pour titre, le programme du Smiley Research Grant. Les informations supplémentaires sur ce sujet seront dans la prochaine édition du Microenvironment.

Surtout, je pense que nous devons tous être fier du rôle que joue chacun d’entre nous étant membre du SCH, en soulignant et encourageant les activités et les réalisations de nos stagiaires et nos professeurs en début de carrière. Au récent Canadien Evening au ASH, un nombre de stagiaires et de professeurs, aussi bien que leurs directeurs et leurs superviseurs, ont été reconnus en les accordant des prix. On en parlera plus dans la prochaine édition de The Microenvironment.

Cette année, la Société canadienne de greffe de cellules souches hématopoïétique (CBMTG) dirigeaient par le Dr Ronan Foley, et le CAG (le Groupe canadien d’aphérèse), dirigeaient par le Dr Gail Rock, va tenir une réunion conjointe, nationale à Toronto du 11 avril, 2012 au 14 avril, 2012. Si cette stratégie portait fruits, nous au CHS aimerait revoir l’idée d’une réunion nationale d’hématologie.

Nous espérons aussi faire une association avec le Dr Catherine Hayward, qui sera l’organisatrice de la réunion en 2013 de la Société Internationale d’Hématologie Laboratoire International (Society of Laboratory Hematology). Il y aura aussi l’occasion d’accueillir la Société internationale d’hématologie (International Society of Hematology - ISH) au Canada, à la réunion en 2016.

En allant de l’avant, j’aimerais vous demander de penser au renouvellement de votre adhésion dans notre organisation nationale importante. Je vous demande aussi de faire connaître le CHS auprès de vos collègues et vos stagiaires. Vous pouvez trouver des informations supplémentaires concernant le CHS sur notre site Internet au www.canadianhematologysociety.org

Sincèrement vôtre,
Stephen Couban, MD
Président, la Société Canadienne d’Hématologie
CHS marks 40 years at recent celebration

The Canadian Hematology Society celebrated 40 years of service to Canadian hematologist practitioners, during the CHS gala evening in December 2011, at ASH in San Diego.

Genesis of the CHS

The early stages of the founding of the CHS are rooted in the constant quandary back in the late 1960s, that Canadian hematologists had no democratic mechanism to choose their own representatives.

Consequently, plans were made for a preliminary meeting to determine whether there was sufficient interest among Canada’s hematologists to organize and address the issue.

Dr. Peter Galbraith undertook the task of writing to those he knew at the academic centres to develop a list of Canadian hematologists, in preparation for the initial gathering, held in Vancouver in January of 1969, at the time of the Royal College Annual Meeting.

Initial meeting

That Vancouver meeting, organized by Wally Thomas, turned out to be a very well attended event, where abundant enthusiasm was evident for the concept of a Canadian Hematology Society.

Those in attendance elected Bernard Cooper to chair a committee to set about the task of establishing an official society to represent hematologists in Canada.

It was this recognition by Canadian hematologists of their acute need for a structured, democratic mechanism for representation at the international level, combined with the positive mandate from the initial Vancouver meeting, that were the driving force behind the foundation of our present-day CHS.

Founding executive

A new era began when fifty-six members gathered on a cold winter day in the Richelieu Room of Ottawa’s Chateau Laurier, on the 20th of January, 1971, and elected Dr. R. Kennedy Smiley, first president of the newly-minted Canadian Hematology Society.

That day delegates also elected Dr. Al Cousineau as vice-president and W. Corbett as secretary-treasurer.

See Page 8, for more photos of CHS 40th Anniversary Celebrations at ASH.

Dr. Peter Galbraith, founding member of the Canadian Hematology Society, makes a ceremonial cut into an anniversary cake, marking the Fortieth Anniversary of the CHS, at a dinner following the AGM, held in conjunction with the ASH meeting in December 2011, San Diego, California. Looking on, Dr. Tom Nevill, CHS President, 2009-2011.

Dr. Galbraith’s undertaking in 1969, to write Canadian academic centres, to develop a list of Canadian hematologists, in preparation for the initial Vancouver meeting in January of that year, was key to the founding of the CHS, which has now grown to represent over 300 members nation wide.

ACKNOWLEDGING OUR CORPORATE SPONSORS

The Canadian Hematology Society gratefully acknowledges the generous and fundamental support contributed by these sponsors in 2011

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The 2011 Canadian Hematology Society Research Award winners, were announced at the CHS Evening at the 53rd ASH Annual Meeting and Exposition on Sunday, December 11, 2011 in San Diego, California.

Members and guests who attended the CHS events enjoyed an excellent opportunity to network in a social setting during a casual reception held at a rooftop lounge, followed by the business meeting, the awards ceremony, and an elegant three-course dinner accompanied by live, instrumental music.

A total of five Research Awards were presented in the categories of PhD and Postdoctoral, Residents and Fellows, and Junior Faculty. The most prestigious of the awards—the John H. Crookston Award—was presented to Dr. Mark Bosch of the University of Calgary. In the photograph on the left, Dr. Bosch, LEFT, is presented the 2011 CHS Crookston Award, by 2010 Crookston Award Winner, Dr. Brent Williams, of the Princess Margaret Hospital, Toronto, Ontario.

2011 John H Crookston Award Winner

Immune Reconstitution After Antithymocyte Globulin-Conditioned Hematopoietic Cell Transplantation.

Dr. Mark Bosch, Department of Medicine, University of Calgary  
(Supervisor: Dr. Jan Storek)

The investigators reported on the results of immune subset analyses performed on 125 allogeneic blood stem cell transplantation (SCT) recipients conditioned with antithymocyte (ATG)-containing regimens and compared these with analyses carried out in 47 patient who did not receive ATG in their conditioning regimen and in healthy donors. Some immune subsets—monocytes, NK cells and dendritic cells—had normalized by 28 days post-SCT in ATG-conditioned patients and by day 180, memory/effector CD8 T cell and naive B cell counts were comparable to healthy donors. However, even on day 730, memory B cells, naive and effector CD4 T cells, naive CD8 T cells, CD4+CD8+ T cells and invariant NKT cells had not yet returned to normal levels. Of interest, immune recovery was different in ATG-conditioned patients compared to those SCT recipients who had not received ATG. At day 28, ATG-treated recipients had lower B cell, CD4 T cell and CD 8 T cell counts than non-ATG recipients but then had a more rapid recovery of total B cells and total CD8 T cells leading to higher counts at day 84. On the contrary, CD4 T cell counts were slower to recover in ATG-conditioned recipient leading to lower counts even at one year post-SCT. Statistical analysis revealed that immune recovery in ATG-treated patients was influenced in various ways by age of the recipient, number of immune cells transferred in the graft, serum ATG levels, recipient CMV serostatus and the development of GVHD.

The value of including antithymocyte globulin in the conditioning regimen prior to allogeneic SCT is an ongoing debate. It may promote engraftment and appears to reduce acute and chronic graft-versus-host disease. On the other hand, it increases the risk of relapse and may lead to more opportunistic infections. These competing outcomes are not surprising as ATG has a profound and complex influence on immune reconstitution following allograft, as this research project elegantly demonstrated.
Conservative Peri-Procedural Anticoagulation Management in Patients with Venous Thromboembolic Disease Results in a Low Proportion of Thrombosis and Bleeding.

Dr. Leslie Skeith, Department of Medicine, London Health Sciences Centre, London, ON (Supervisor: Dr. Michael Kovacs)

This study examined the incidence of venous thromboembolic (VTE) disease in patients on chronic anticoagulation for a history of VTE in the first 3 months following a surgical procedure. The study cohort included 416 patients that underwent 634 procedures between 1993 and 2011 with a standardized approach of stopping oral warfarin 5 days pre-operatively with no low molecular weight bridging therapy. Patients had warfarin re-started as soon as they could swallow and LMW heparin was used as post-operative bridging only if patients required post-operative hospitalization (~25% of the procedures) and, even then, only received heparin until the INR was therapeutic or the patient was fit for hospital discharge. The incidence of VTE at 3 months post-operative was only 0.63% (4 patients with DVT; no PE was observed and there were no VTE deaths in the patient cohort). The incidence of any bleeding and major bleeding was 1.6% and 3.5%, respectively. There were significantly higher proportion of inpatients in the total bleeding event group (p=0.04) and a significant correlation between bleeding events and VTE events-- almost 1/3 of the patients with a major bleeding event had a DVT as well.

While guidelines for peripoperative management of anticoagulation in individuals at moderate or high risk for VTE generally include bridging with LMW heparin, there is limited literature support for this approach and post-operative bleeding remains a risk. This retrospective study demonstrates the exceedingly low risk of VTE when a conservative anticoagulation approach is used in patients on long-term warfarin for a history of VTE.

A Gene Expression Signature in Diagnostic Formalin Fixed Paraffin Embedded Tissue Predicts Overall Survival in Locally Advanced Stage Classical Hodgkin Lymphoma – a Correlative Study From the E2496 Intergroup Trial.

Dr. David Scott, Centre for Lymphoid Cancer, British Columbia Cancer Centre (Supervisor: Randy Gascoyne)

The investigators in this study employed NonoString technology to quantitate 261 mRNA species from genes known to influence outcome in classical Hodgkin Lymphoma (cHL) in paraffin embedded specimens obtained from 293 patients in a large Intergroup trial. A prognostic model was generated from this analysis and was tested in a separate group of 130 patients with advanced stage cHL enriched for treatment failure. Of the 293 patients examined from the Intergroup trial, 36 (12%) had died with 51 genes differentially expressed in this cohort. A predictive model was generated from this gene expression profile that allowed for the identification of a low-risk [Overall survival (OAS) of 96% at 5 years] and a high-risk group (OAS of 77% at 5 years). This model was validated in the separate cohort of 130 patients with an OAS of 91% and 71%, respectively.

This paper provides a gene-expression-based predictor of OAS in cHL patients treated with standard induction chemotherapy. This may offer an alternative to the International Prognostic Score that is currently used and could be more useful in identifying individuals in which high-dose therapy or targeted treatments may be considered in order to further improve outcome in this disease.
2011 Junior Faculty Research Award

Inactivating Gene Alterations of MHC Class II Transactivator CIITA Are Recurrent in Primary Mediastinal B Cell Lymphoma and Hodgkin Lymphoma.

Dr. Christian Steidl, Department of Pathology and Laboratory Medicine, British Columbia Cancer Agency, Vancouver, BC.

This research focussed on studying alterations in the CIITA gene through whole transcriptome paired-end sequencing and single nucleotide polymorphism arrays. The investigators evaluated the CIITA gene with this technique in 3 primary mediastinal B cell lymphoma (PMBCL) cell lines, 9 Hodgkin lymphoma (HL) cell lines and 23 PMBCL tissue samples. They were able to demonstrate that chromosomal deletions and rearrangements affected both CIITA alleles in both PMBCL and HL cell lines. Small intronic deletions and single nucleotide mutations in CIITA Intron 1 were demonstrated in 43% of the PMBCL tissue samples but none of 18 large cell lymphoma specimens and none of 15 reactive lymph node specimens. The CIITA rearrangements, deletions and mutations led to significantly lower CIIA and HLA-DR expression. It is postulated by the authors that this may promote immune escape of the tumour cells in PMBCL and HL.

Our understanding of the genetics of tumour cells continues to expand at an exponential rate. This fascinating research provides a clear link between loss of tumour cell immunogenicity and the development of lymphoma. It is not unreasonable to expect that this will lead to new “targeted” therapies although the underlying cause of these genetic alterations remains a mystery.

Mir-34a Sensitizes Multiple Myeloma Cells to the Proteosome Inhibitor Bortezomib

Erin Stebner, Ph.D, University of Calgary, Calgary, AB
(Supervisor: Dr. Nizar Bahlis)

MicroRNA (miRNA) are small non-coding RNAs that regulate messenger RNA. Their deregulation can lead to the development of malignancy and miRNAs have been linked to both the clonal evolution of plasma cells and to growth inhibition in multiple myeloma. The investigators performed microarray profiling of miRNA signatures in multiple myeloma cell lines that possessed different sensitivities to Brotezomib. They found that the cell lines could be divided into two distinct subgroups with “sensitive” cell lines demonstrating much higher expression of mir-34a compared to resistant cell lines. The resistant cell lines all had mutations in TP53 and were also shown to have promoter methylation with treatment with Azacitidine leading to upregulation of mir-34a. Further studies were able to show that lentivirus-mediated expression of mir-34a in the resistant cell lines significantly increased their sensitivity to Bortezomib. Subsequent murine experimentation confirmed that this upregulation of mir-34a had a real effect on myeloma tumour growth.

This elegant series of experiments serve to increase our knowledge of the complex biology of multiple myeloma. The treatment algorithm for MM has become much more complicate over the past 5 years and there has been a tremendous explosion of targeted treatments available for this patient population. It may be that agents designed to upregulate mir-34a will be another therapeutic choice that clinicians will be able to add to their armamentarium in the future.
**Q** Your Hematology interest is in clinical thrombosis research. How did you get interested in this area?

**A** “I got interested in venous thrombosis as a medical resident at Dalhousie. I admired the quality of research in this field that was done at McMaster. When I went to McMaster to do my hematology fellowship I was fortunate enough to get further exposure to the field and was influenced by the world class leaders that I worked with such as Jack Hirsh, Mark Levine, Jeff Weitz and Jeff Ginsberg. I was also encouraged by our program director John Kelton to seek the opportunities that an academic career offered.”

**Q** What is the key to being successful at clinical research?

**A** “Success at clinical research does depend on the interest and drive of the individual. But perhaps as important are getting excellent research training and having good mentorship and collaborative research opportunities. I have been very fortunate to have worked with a very strong collaborative national research group that includes Phil Wells, Marc Rodger and Marc Carrier in Ottawa, Michael Kovacs in London and Susan Kahn in Montreal.

**Q** You are now the Head of the Department of Medicine. What motivated that change and how has the job changed your work in hematology?

**A** “Department head poses new challenges and opportunities. It has allowed me the opportunity to influence the careers and activities of a large number of faculty which I find very rewarding. My primary job now is to help them succeed and grow their areas of interest. I have had to step back in my hematology work but I have been fortunate to have colleagues who have stepped into our thrombosis program at Dalhousie and are working to build upon and improve the programs I had some role in starting.

Stephen Couban as Division Head, Sue Robinson and Sudeep Shivakumar my colleagues with a major interest in thromboembolism have been instrumental in making this transition smooth for myself and patient care.”

**Q** In your spare time you are quite a good golfer. Could you have made a career of it?

**A** “Over the years I have switched my sporting focus to tennis. Great for fitness and focus. Now that my children are older I plan to play a bit more golf and maybe challenge Tom Watson—I mean Nevill—someday!”

**WHAT IS THE DIAGNOSIS?**

- An 18 year-old, previously entirely healthy, Asian woman presented with a 4-day history of headache, fever of 41 degrees C, lightheadedness and diarrhea.
- She was jaundiced but did not have any lymphadenopathy or hepatosplenomegaly on physical examination.
- Her CBC showed a hemoglobin of 94 g/L, WBC of 15.7 x 10^9/L (90% neutrophils) and platelets of 76 x 10^9/L.
- Total bilirubin was 226 umol/L and direct bilirubin 163 umol/L; AST was 539 U/L, ALT 196 U/L and LDH 3244 U/L. Serum ferritin was 42,000.
- A bone marrow examination was done (see picture).
- What is the diagnosis?

*(ANSWER: bottom of page 14.)*
Incoming CHS President, Dr. Stephen Couban

Welcome to the Annual CHS Reception Awards Presentation and Dinner Celebrating our 40th Anniversary 6:30 pm

Incoming CHS President, Dr. Stephen Couban

2011 CHS Research Abstract Award Winners, FROM LEFT, Junior Faculty, Dr. Christian Steidl; PhD & Post Doctoral, Dr. Erin Stebner; Residents & Fellows and Winner of the John H. Crookston Award, Dr. Mark Bosch; Residents & Fellows, Dr. Leslie Skeith; and PhD and Post Doctoral, Dr. David William Scott.

CHS 40th Anniversary Gala Evening

Dr. Peter Galbraith, Founding Member and CHS Past President

Dr. Tom Nevill, CHS President, 2009—2011

Guests enjoy the CHS Reception at a rooftop lounge, overlooking San Diego’s historic Gaslamp Quarter.

Dr. Gail Rock

CHS Evening at ASH - a great networking opportunity

CHS Members vote in support of the new executive during the AGM, Sun., Dec. 11, 2011 in San Diego

Dr. Aaron Schimmer
Hemophagocytic lymphohistiocytosis in adults

Luke Chen, MD, FRCPC
Clinical Assistant Professor,
University of British Columbia
lchen2@bcca.ca

Case:

- A previously healthy 54 year old Chinese female presented with a ten month history of fever, sweats and 10 kg weight loss.

- Labs revealed PMNs 1.3 giga/L, hemoglobin 120 g/L, platelets 110 giga/L, INR 1.2, PTT 47s (24-40s), fibrinogen 2.0 g/L, creatinine 92 μmol/L, total bilirubin 11 μmol/L, ALT 94 U/L, AST 106 U/L, GGT 171 U/L, ALP 635 U/L, LDH 631 U/L (< 240 U/L).

- Serum ferritin was 39, 789 μg/L. CT of the chest, abdomen and pelvis revealed splenomegaly (15 cm) and retroperitoneal lymphadenopathy.

- She underwent a core needle lymph node biopsy which revealed a polymorphous infiltrate of large T cells (EBV EBER positive) but PCR for T cell receptor clonality was negative.

- A bone marrow biopsy revealed an atypical T cell infiltrate and prominent hemophagocytosis. Peripheral blood EBV DNA level was 373 000 copies/mL and the patient was diagnosed with EBV-associated hemophagocytic lymphohistiocytosis.

Discussion: Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder of pathological immune activation leading to profound inflammation and immune-mediated pathology such as cytopenias, hepatitis, coagulopathy, and hemophagocytosis. Most of our knowledge of this disease, including the standard diagnostic criteria (Table 1) is derived from the pediatric population, for which international collaborative efforts have dramatically improved long term survival.

The literature on adult HLH is scant, and suggestive of very poor outcomes. HLH can occur as a “primary” disorder, typically in children with a known genetic cause or family history, or as a ”secondary” condition associated with known predisposing and/or triggering factors. Predisposing factors include primary or acquired immunodeficiency, malignancy (particularly lymphoproliferative disorders), and autoimmune disease.

Known triggers of HLH include infections, particularly EBV, and medications such as etanercept and alemtuzumab (which ironically is also used to treat HLH).

Given the rapid progression and high mortality of this disease, prompt diagnostic evaluation and initiation of therapy are essential. Emmeneger has proposed that patients presenting with SIRS, cytopenias, and a known predisposing or triggering factor for HLH be screened with a serum ferritin.

A ferritin of > 3000 μg/L is suspicious for HLH, and > 10 000 μg/L is quite specific. Patients with hyperferritinemia should proceed to bone marrow, liver, or lymph node biopsy, testing for HIV, EBV and CMV, and consideration of specialized testing for HLH.
Once diagnosed, patients fit for treatment should begin chemoimmunotherapy immediately. Etoposide, which has activity against monocytes/macrophages, is the backbone of therapy in the HLH 2004 protocol and is combined with high dose dexamethasone and cyclosporine.

Early administration of etoposide, even in the setting of severe cytopenias and hepatic dysfunction is crucial, although dose reduction for renal impairment may be necessary. Anti-thymocyte globulin and alemtuzumab have also been used for initial treatment and for relapsed/refractory disease, and rituximab has been employed to eradicate EBV-infected B cells. Outcomes of the Histiocyte Society treatment protocols have only been reported in pediatric patients.

Applying these protocols, and in particular their emphasis on consolidative allogeneic stem cell transplant, is an extrapolation requiring clinical judgement. In our experience, treatment in frail, elderly, or multiply impaired patients improves laboratory parameters such as ferritin and viral load, but not clinical outcomes, and palliation in these situations is reasonable. For patient who responded to initial therapy, specialized tests may be helpful in prognosis and deciding whether allogeneic stem cell transplant is necessary. These include molecular genetics for known HLH and XLP associated mutations, NK cell function, soluble CD25, and CD107a mobilization, and are available at specialized centers such as Toronto’s Sick Kids Hospital and Cincinnati Children’s Hospital.

The patient in the case above responded initially to etoposide-based therapy, but relapsed four months after diagnosis and died despite salvage therapy with alemtuzumab.

Acknowledgements: I would like to thank my colleagues in Pediatric Hematology/Oncology (the real HLH experts!), particularly Dr.’s Kirk Schultz and David Dix (BC Children’s Hospital) and Dr. Sheila Weitzman (Sick Kids Hospital) for their advice on the patients that I have cared for.

**Case:**
- A 40 year old woman with a history of having been treated for aplastic anemia with immunosuppressive therapy (IST) 5 years previously is referred for re-assessment.

- She now complains of fatigue as well as intermittent abdominal discomfort lasting for a few hours at a time.

- She has not noticed any blood in her stool or change in bowel habits.

- She also has episodes of back discomfort associated with passage of dark coloured urine which clears as the day progresses.

This patient’s symptoms of fatigue, probable hemoglobinuria and intermittent abdominal pain are suspicious for the development of Paroxysmal Nocturnal Hemoglobinuria (PNH).

This rare acquired disorder has an annual incidence of 2 - 10 cases/million and it is estimated that each year there are about 100 newly diagnosed patients in Canada. Previous IST for aplastic anemia (AA) increases the risk of developing PNH (up to 10% of patients at 10 years), as well as MDS, and patients may also develop recurrent aplasia years after treatment. PNH can be classified as primarily hemolytic (classic), associated with aplasia (AA/PNH) or subclinical (typically with a clone of <10%).

Relevant to the case described, current recommendations support that annual PNH testing be performed in the setting of previous IST for AA. Flow cytometric analysis of peripheral blood granulocytes (for CD55, CD59 and FLAER) has replaced the more traditional Hams and Sucrose Lysis tests and is capable of detecting and quantifying small clones. Recently, guidelines for flow cytometry testing for PNH have been published.

PNH patients have a high incidence of thrombosis and require a careful evaluation for thrombotic complications as well as documentation of severity of hemolysis and assessment of major organ function.

Treatment must be individualized and patients with small clones may only require regular, ongoing monitoring. In the past, treatment options for PNH patients were limited to the use of steroids (primarily for amelioration of acute hemolytic episodes), erythroid stimulating agents, androgens, judicious iron and folate supplementation and anticoagulation.

A number of experienced clinicians had suggested that prophylactic anticoagulation be initiated when the PNH granulocyte clone exceeded 50%. More recently, prophylaxis has only been recommended when D-Dimers are persistently positive. While thrombotic events in PNH patients can occur at conventional sites (DVT/PE), they not infrequently develop at unusual sites (e.g. superior sagittal vein, hepatic vein or mesenteric vessels).

Hemolysis of PNH cells is a consequence of complement-mediated cytolysis and inhibition of complement was thought to be a logical approach to therapy in this patient population. Eculizumab (Soliris®) is a humanized monoclonal antibody against complement C5. It binds specifically to C5, thereby preventing the formation of the terminal complement complex C5b-9, which mediates cell lysis.

Several multicentre international clinical trials have shown it to be effective in PNH patients in reducing...
hemolysis and transfusion needs, improving quality of life and, as a secondary finding, in reducing risk of thrombosis.\textsuperscript{3-5} Eculizumab was approved by Health Canada in January 2009, by Common Drug Review in February 2010 and funded in many provinces in July 2011.

Because it is a costly medication, is non-curative and is used indefinitely in those patients that respond, strict criteria for its approved use have been established by the funding bodies. These criteria include: (1) confirmation of hemolytic PNH with a granulocyte clone >10% and LDH >1.5 times ULN; (2) no evidence of ongoing marrow aplasia; and (3) at least one of the following: thrombosis requiring anticoagulation, transfusion dependence (≥ 4 units in last 12 months), anemia (one hemoglobin <70 g/L or multiple hemoglobins <100 g/L), pulmonary insufficiency, renal insufficiency or smooth muscle spasm requiring narcotic analgesia or hospitalization.

Proof of patient consent and meningococcal vaccination (2/52 pre-treatment) are required for funding to be approved and reevaluation is required every six months. Responding patients in the original Eculizumab trials had reductions in thrombotic events and had normalization of D-Dimer levels. Hence, discontinuation of prophylactic anticoagulation may be considered in some patients though this has not been formally studied.

Eculizumab is given intravenously once weekly at 600mg for 4 doses then as indefinite maintenance at 900mg every 2 weeks. Patients are monitored initially with CBC, reticulocyte count, bilirubin, and LDH. The LDH often normalizes quickly and patients generally feel better early in the treatment course. The reticulocyte count rarely normalizes and the hemoglobin response is variable although the majority of anemic patients become transfusion-independent.

If the hemoglobin does not improve by 2–3 months, investigations for breakthrough hemolysis with biochemical parameters and pharmacokinetic studies are recommended. If suboptimal drug levels are confirmed, the infusion interval can be shortened to every 12 days. Less than optimal responses have also been observed as a result of extravascular hemolysis and alternate treatments may be required including danazol, low-dose prednisone, erythroid stimulating agents and even splenectomy. Discontinuation of Eculizumab requires careful monitoring for several weeks to ensure that life-threatening hemolysis does not develop.

Stem cell transplantation remains the only curative treatment for PNH and is generally reserved for young patients with a suitable HLA-compatible donor in the context of severe cytopenias or, in the Eculizumab era, patients with severe hemolysis or those that have had a life-threatening thrombotic event.

References:
ISLH Returns to Canadian roots in 2013

Submitted by
Dr. Catherine Hayward
Executive Secretary, ISLH

The International Society of Laboratory Haematology (ISLH) the largest international organization dedicated to serving the interests of the laboratory hematology community worldwide, is excited to be holding its XXVIth International Symposium on Technological Innovations in Laboratory Hematology in Laboratory Hematology in Toronto on May 9-12, 2013.

Canadian Origins
Canada has had an important place in ISLH history as the inaugural “Technical Innovations in Laboratory Hematology” was held in Banff in 1984. This first meeting in Canada led to the foundation of ISLH as a non-profit organization in 1992.

Since its initial founding by Dr. Berend Houwen and Dr. Bruce Davis, ISLH has evolved to a growing, international organization of more than 700 members, representing over 50 countries, and holds its annual scientific meetings in many different corners of the globe.

Annual Conference Benefits
The annual conference showcases exciting advances in laboratory hematology, with state-of-the-art topics covered in multiple plenary and concurrent sessions and in abstract presentations.

Members consider ISLH “the very best meeting to get updates on advances, standards and best practices across the spectrum of laboratory hematology” including: cellular analysis, flow cytometry, hemostasis and thrombosis, molecular diagnostics, hemoglobinopathies and red cell disorders, point of care testing and standards and guidelines.

Current Board


Membership Welcomed
The ISLH Board welcomes all professionals in laboratory hematology to join and enjoy the privileges, opportunities and benefits of belonging to the only international society dedicated to meeting the needs of the laboratory hematology community.

ISLH has been instrumental to the development of standards and guidelines in the field of laboratory hematology and it has strong ties to the International Committee for Standardization in Hematology (ICSH) which participates in ISLH meetings.

Benefits of Membership
ISLH members receive discounted registration for the ISLH annual scientific meeting (International Symposium on Technological Innovations in Laboratory Hematology – a fantastic opportunity to network with peers), a subscription with online access to IJLH, priority notification of ISLH activities and programs and meeting material postings.

The 2013 ISLH meeting in Toronto represents a wonderful opportunity for the Society to return to Canada where it all began. Non-members who attend the 2013 ISLH conference will receive complementary membership for 2013.

Scientific Program
The Toronto meeting has received strong and valued support from the Canadian Hematology Society to advance laboratory hematology. Dr. Marciano Reis (Toronto), and Dr. Betsy Van Cott (Boston), are leading the program development as the 2013 ISLH Scientific Program Co-chairs.

... continued on Page 13
Other organizations that are supporting the meeting include: the North American Specialized Coagulation Laboratory Association (NASCOLA, an organization with many Canadian members that partnered with ISLH for its highly successful 2009 and 2011 meetings; NASCOLA leadership includes Dr. Van Cott –President, Dr. Hayward – Immediate Past-President); the Quality Management Program – Laboratory Services in Ontario, which will host an exciting, pre-ISLH, half day meeting to cover hot topics in quality assurance for hematology laboratories, open to all in 2013 ISLH registrants; the Canadian Society of Medical Laboratory Sciences; and the Association des médecins hématologues et oncologues du Québec.

ISLH looks forward to working with the Canadian Hematology Society to make the Toronto meeting a record success.

Members of the Canadian Hematology Society should feel welcome to contact:

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haywrde@mcmaster.ca

and

Dr. Reis:
Marciano.Reis@sunnybrook.ca

about the ISLH 2013 meeting.

...continued from Page 13

“The 2013 ISLH Toronto meeting is a wonderful opportunity for the Society to return to Canada where it all began.

Non-members who attend the 2013 ISLH conference will receive complementary membership for 2013.”

Upcoming Events

- The Canadian Hematology Society Annual Reception, Awards Presentation & Dinner, will be held (during ASH) Sunday December 9, 2012, in Atlanta GA.
  
  For more information: chs@uniserve.com

- The American Society of Hematology (ASH) 54th Annual Meeting and Exposition, will be held December 8 – 11, 2012, in Atlanta GA.
  
  For more information: www.hematology.org

- The Canadian Bone Marrow Transplant Group (CBMTG) April 10—13, 2013, Fort Garry Hotel, Winnipeg, Manitoba.
  
  For more information: www.cbmtg.org

- International Society of Laboratory Hematology (ISLH) Toronto, 2013 Members of the Canadian Hematology Society should feel welcome to contact:

  Dr. Haywayrd
  haywrde@mcmaster.ca

  and

  Dr. Reis:
  Marciano.Reis@sunnybrook.ca

  about the ISLH 2013 meeting.

...from Page 3: WHAT IS THE DIAGNOSIS?

The Answer:

The bone marrow exam (and the exceedingly high ferritin) are consistent with Hemophagocytic Lymphohistiocytosis (HLH). She was negative for HIV Ag/antibody, hepatitis B surface Ag and core antibody and hepatitis C RNA and antibody.

However, she was strongly positive for CMV IgM antibody and CMV PCR was positive on the peripheral blood. She was treated with Ganciclovir and the HLH 2004 protocol consisting of Etoposide, Cyclosporine and Dexamethasone.

Her symptoms rapidly improved and her hepatic function normalized over a three week period; she remains on a tapering dose of Cyclosporine. Molecular testing for known familial HLH mutations was negative.
**Transfusion Medicine Specialist (General) in Melbourne or Perth, AUSTRALIA**

The Australian Red Cross Blood Service has TWO exciting opportunities—one in Perth and one in Melbourne. If you are an experienced Haematologist or recently qualified—if you have an interest in Transfusion Medicine we would like to hear from you.

The position reports in to the National Transfusion Specialist and exists to provide Transfusion Medicine specialist advice to internal staff and external stakeholders to ensure appropriate clinical risk management and a patient-focused management of blood/blood products. Close liaison with government bodies and clinicians outside the Blood Service are also key to the role.

**Qualifications**

- **Essential:** Medical Degree—MRCP, FRCPath, FRACP, FRCPA or equivalent.
- **Desirable:** Fellowship with other specialist college or equivalent
- **Experience:** Haematology, Blood Banking, Transfusion Medicine or relevant field

**Key skills**

- Initiative, problem-solving, communication, customer-service led, awareness of the issues with running a Blood Service and QA procedures

**Key responsibilities**

- Provide expert medical advice within the Blood Service, medical and health facilities:
  - Quality Manufacturing procedures oversight
  - Patient Blood Management
  - Product and Services support
  - Research
  - Oversight of Laboratory
  - Customer Service
  - Education

If you are a collaborative, self-motivated, team-oriented and professional medical specialist then we would like to hear from you.

If you would like to know more, please call or email:

Graham Parcell (Senior Consultant)  OPAL Executive Search, Adelaide, Australia
Telephone: 00 61 8 8276 7159 or 00 61 8 408 600 097  Email: gp@opalsearch.com

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**Thrombosis Fellowship 2012-2013**

**Jewish General Hospital, McGill University, Montreal, Quebec**

The JGH Thrombosis Program is currently accepting applications for a one year fellowship (July 1, 2013 - June 30, 2014) to acquire and consolidate expertise in Thrombosis. Specific areas of clinical activity include the Thrombosis Clinic, Anticoagulation Clinic and In-patient Thrombosis Consultation Service.

Our Thrombosis Program also encompasses a broad range of research activities that relate to diagnosis, risk factors and treatment of venous and arterial thromboembolic disease.

For information, please contact: Dr. Susan Kahn
514-340-7587
susan.kahn@mcgill.ca

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**Thrombosis Clinical & Research Fellowships - Up to 3 positions**

Applications are encouraged from MDs who have completed or who will complete General Internal Medicine, Respiratory and/or Hematology training. Foreign medical graduates with equivalent qualifications are eligible.

Applicants may apply to one of three training streams:

1.) **Clinical Fellowship**, one-year—To consolidate expertise in thrombosis.

2.) **Clinical and Research Fellowship**, 2-3 years (to become a clinician investigator in thrombosis (Fellows enroll in the Master’s of Clinical Epidemiology Program at the University of Ottawa).

3.) **Clinical and Education Fellowship**, 2-3 years (to become a clinician educator in Thrombosis. (Fellows enroll in a Master’s in Education).

To apply, please contact: nlanglois@ohri.ca

Details are also available on the CHS website.
Membership Matters

The Canadian Hematology Society has represented all physicians and scientists with an interest in the discipline in Canada since its founding 40 years ago in 1971. Our society now has over 300 members.

Active Membership is open to physicians engaged in the practice of clinical or laboratory hematology in Canada and to any persons doing scholarly research in hematology in Canada.

In appropriate cases, the requirement for a university degree or other qualifications may be waived if in the opinion of the Executive Committee the candidate is making significant continuing contributions to science.

We welcome residents and fellows in approved university training programs in hematology or hematological pathology as Associate Members. Associate members will not be required to pay dues until the completion of training.

Emeritus Membership is open to individuals at the age of 65 or those who were active members and request a transfer of status with adequate reason. Emeritus members will not be required to pay a membership fee.

Non-members may be invited to become Honorary Members of the Corporation by virtue of their outstanding contributions to any discipline which is of importance to hematology.

CHS members are reminded ...

to please remit your 2012 Annual Dues. Your $75. annual dues payment may be made online at the CHS website: www.canadianhematologysociety.org

Or mailed to: Canadian Hematology Society, 199-435 St. Laurent Blvd., Ottawa, Ontario K1K 2Z8

Please provide the following information with your payment:

2012 Membership Renewal: Canadian Hematology Society

Name: ______________________________________

Membership Status

Active □
Associate □
Emeritus □

Title: ______________________________________

Email: _____________________________________

Work Address:________________________________

Has your status changed?

Yes □
No □

Work Phone: ________________________________

Work Fax: ________________________________