Cotyledonoid Dissecting Leiomyoma of the Uterus

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Canadian Journal of Pathology

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www.andrewjohnpublishing.com/CJP/instructionstoauthors.html

About the Cover

A tangential section of Descemet's membrane (bovine), the basement membrane of the corneal endothelium, reveals a hexagonal array of nodes and filaments with a distance of 110 nm between nodes (Bruns and Heathcote, 1982, unpublished).

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It is with great pleasure that I take over the direction of the new Canadian Journal of Pathology from its founding editor, Dr. Jagdish Butany. All of us in pathology and laboratory medicine in Canada, whether or not we are members of the Canadian Association of Pathologists (CAP-ACP), owe Dr. Butany a great debt of thanks for his achievement in creating this journal. It is more than 25 years since the idea of a national pathology journal was first raised, and it is to the credit of Dr. Butany and his colleagues on the executive of the CAP-ACP that this has finally been accomplished.

Given the spotlight that has been thrown on pathology in several provinces over the past few years, we are fortunate that we now have a publication that can project the quality and importance of our work nationally and, I hope some day, internationally.

In assuming the role of editor-in-chief, my goals are straightforward:

- To enhance the reputation of Canadian pathology
- To attract manuscripts of high quality dealing with the scientific, technical, conceptual, and administrative aspects of all disciplines within pathology and laboratory medicine
- To strengthen the cohesion among Canadian pathologists and laboratory physicians and bring the importance of our work to the attention of government, as well as the wider medical and scientific communities
- To ensure that the journal contains material of interest to all pathologists, laboratory physicians, and scientists

It will not always be easy to achieve these goals, and a delicate balance will need to be struck between catering to the everyday interests of members of the CAP-ACP and developing a journal with a reputation for quality papers.

My first priority as editor-in-chief has been to establish an editorial board that will provide expert guidance in all areas of our discipline. Brief biographies of the colleagues who have agreed to serve on the editorial board are provided on page 7 and on the publisher’s website (www.andrewjohnpublishing.com). I know them all to be meticulous and committed, and I am grateful to them for accepting my invitation to serve the journal. I am particularly pleased that we have been able to select a section editor for quality and informatics since these are areas that need to be emphasized.

I am also delighted that a medical biochemist with an interest in cancer biomarkers and a virologist have agreed to join the board. At least on the research front, many of the laboratory disciplines are moving closer together, and greater communication among all laboratory colleagues will only benefit patient care, research, and teaching.

Over the next few months, the editorial board and I will be working to establish content standards and guidelines, and the current “Instructions for Authors,” available on the publisher’s website, will be revised. I hope that the named lectures given at the annual meeting of the CAP-ACP will be published each year to strengthen the journal’s linkage with its professional sponsor. The speakers from the 2009 meeting in Halifax have agreed to submit their lectures, with the William Boyd Lecture published in this issue, and this is a precedent that I hope others will be keen to follow. For success, the whole community of Canadian pathology and laboratory medicine must support its journal. One of the most challenging tasks for any editor is finding reviewers for manuscripts, and I hope that everyone will see it as part of their professional responsibilities when asked for assistance in this. Pathologists, like other physicians and scientists, want their good work to be published in reputable journals with a wide readership, and I encourage the Canadian chairs of pathology and laboratory medicine to set an example for their postgraduate trainees and graduate students by supporting the journal. With commitment, I am confident that our journal can find a niche among other, more established specialist journals.

Initially, the journal will be published four times a year. As we try to establish the journal’s own style and character, there will be room for some experimentation. At all times, I will be pleased to receive your comments and suggestions about how we can make the journal better.

J. Godfrey Heathcote
Editor-in-Chief
J’ai accepté avec un grand plaisir d’assumer la direction de la nouvelle *Revue canadienne de pathologie* et de prendre la relève du rédacteur en chef fondateur, le Dr Jagdish Butany. Tous les acteurs du milieu de la pathologie et de la médecine de laboratoire, membres ou non de l’Association canadienne des pathologistes (ACP), sont extrêmement redevables au Dr Butany pour ses réalisations. L’idée de lancer une revue nationale de pathologie remonte déjà à plus de 25 ans, et c’est grâce au Dr Butany et à ses collègues du bureau de l’ACP qu’elle a pu être concrétisée. Étant donné que la pathologie a été propulsée sous les feux de l’actualité dans plusieurs provinces ces dernières années, nous avons de la chance d’avoir maintenant une publication pour refléter la qualité et l’importance de notre travail à l’échelle nationale et, je l’espère un jour, à l’échelle internationale.

En tant que nouveau rédacteur en chef, je vise des objectifs concrets :

- Améliorer la réputation de la pathologie au Canada
- Attirer des manuscrits de grande qualité qui traitent des aspects scientifiques, techniques, conceptuels et administratifs de l’ensemble des disciplines relevant de la pathologie et de la médecine de laboratoire
- Renforcer la cohésion entre les pathologistes et les médecins de laboratoire canadiens et sensibiliser le gouvernement et les acteurs du milieu scientifique et médical à l’importance de notre travail
- Veiller à ce que la Revue contienne du matériel d’intérêt pour l’ensemble des pathologistes, des médecins de laboratoire et des scientifiques

L’atteinte de ces objectifs ne se fera pas sans effort. Il faudra assurer un équilibre délicat entre la nécessité de veiller aux intérêts quotidiens des membres de l’ACP et celle de bâtir une revue qui se démarque par la qualité de ses articles.

En tant que rédacteur en chef, ma préoccupation première a été de constituer un comité de rédaction capable de nous fournir des conseils d’experts dans tous les secteurs de notre discipline. Vous trouverez une brève biographie des collègues qui ont accepté de siéger à ce comité à la page 7 et dans le site Web de l’éditeur (www.andrewjohnpublishing.com). Je sais qu’ils sont tous très méticuleux et dévoués. Je leur suis reconnaissant d’avoir accepté mon invitation à collaborer à la Revue. Je suis particulièrement heureux que nous ayons pu trouver un rédacteur pour la section sur la qualité et l’informatic. Ces deux sections ont besoin d’être mises en valeur. Je suis également ravi qu’un virologiste ainsi qu’un biochimiste médical ayant un intérêt particulier pour les biomarqueurs de cellules cancéreuses aient consenti à se joindre aux membres du Comité de rédaction. Dans nombre de disciplines de laboratoire, les intérêts continuent de se rapprocher, du moins du côté de la recherche. L’amélioration des communications entre les collègues de ces disciplines ne pourra qu’avoir des retombées positives sur les soins aux patients, la recherche et l’enseignement.

Au cours des prochains mois, les membres du comité de rédaction et moi-même travaillerons à établir des normes et des directives relatives au contenu de la Revue. Nous réviserons également les « Directives pour les auteurs » disponibles dans le site Web de l’éditeur. De plus, je souhaite que les conférences présentées par les invités d’honneur à l’assemblée annuelle de l’ACP soient publiées chaque année afin de renforcer le lien entre notre Revue et son parrain professionnel. Les invités d’honneur à l’assemblée qui a eu lieu à Halifax en 2009 ont d’ailleurs accepté de nous transmettre leur conférence. Celle portant sur William Boyd est publiée dans le présent numéro. Cette initiative constitue un précédent qui, je l’espère, en inspirera plus d’uns parmi vous. Pour que sa Revue soit une réussite, l’ensemble du milieu canadien de la pathologie et de la médecine de laboratoire doit se mobiliser.

L’une des tâches les plus difficiles d’un éditeur consiste à trouver des réviseurs pour les manuscrits. J’espère que lorsque nous ferons appel à vous dans ce but, vous considerez que cela fait partie de vos responsabilités professionnelles. Les pathologistes, comme les autres médecins et scientifiques, veulent que leurs travaux soient publiés dans des revues renommées qui jouissent d’un vaste lectorat. J’encourage les directeurs des programmes de pathologie et de médecine de laboratoire canadiens à montrer l’exemple à leurs étudiants de deuxième et de troisième cycle en appuyant la Revue. Je suis sûr qu’avec de la détermination, notre Revue saura trouver un créneau parmi les autres revues spécialisées déjà établies.

Au départ, la Revue sera publiée quatre fois par année. Pendant que nous travaillerons à en établir le style et les caractéristiques, il y aura place à l’expérimentation de certains concepts. En tout temps, je serai heureux de recevoir vos commentaires et vos suggestions en ce qui a trait à l’amélioration de la Revue.

J. Godfrey Heathcote
Rédacteur en chef
Meet the Members of the CJP Editorial Board

J. Godfrey Heathcote, MA, MB BChir, PhD, FRCPC
Editor-in-Chief
Godfrey Heathcote graduated in biochemistry from the University of Cambridge. During residency training in anatomical pathology at the University of Western Ontario, he studied ophthalmic pathology, which has since become his primary focus. In 2004, he was appointed head of the Department of Pathology at Dalhousie University and chief of pathology and laboratory medicine for the eight laboratories of the Capital District Health Authority in Halifax, Nova Scotia. Since 1994, he has been the section editor of general and ophthalmic pathology for the Canadian Journal of Ophthalmology, and was a member of the editorial team responsible for the publication in 2008 of the third edition of Garner and Klintworth’s Pathobiology of Ocular Disease.

Manon Auger, MD, FRCPC
Section Editor, Cytopathology
After obtaining her MD degree at McGill University, Manon Auger completed her residency training in anatomical pathology at the University of Toronto, followed by a cytopathology fellowship at the University of Texas M.D. Anderson Cancer Center. She is currently director of the Cytopathology Laboratory at the McGill University Health Centre and is an associate professor in the Department of Pathology at McGill University. Dr. Auger has given numerous cytopathology workshops in Canada and the United States and is the course director of the annual McGill Cytopathology Review Course.

Calvino Cheng, BSc, MD, FRCPC
Section Editor, Pathology Informatics and Quality Management
Calvino Cheng graduated in biochemistry and medicine from the University of Calgary. Since 2005, he has been a staff hematopathologist at the Queen Elizabeth II Health Sciences Centre and the Capital District Health Authority in Halifax, where he is the medical director of the Pathology Informatics Group. He is an assistant professor of pathology at Dalhousie University and director of the hematopathology residency training program. His major interests lie in transfusion medicine, laboratory utilization, and pathology informatics, and he is an adviser to the Canada Health Infoway project.

Eleftherios Diamandis, BSc, MD, PhD, FRCPC
Section Editor, Medical Biochemistry
Following a degree in chemistry from the University of Athens, Eleftherios Diamandis trained in medicine and clinical biochemistry. Since 1995, he has been head of clinical biochemistry at Mount Sinai Hospital in Toronto, and is currently professor and head of the Division of Clinical Biochemistry in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. Dr. Diamandis is actively engaged in research in cancer biomarkers and molecular diagnostics. He serves on the editorial boards of a number of journals, including British Journal of Cancer and Molecular Oncology.

David K. Driman, MB ChB, FRCPC
Section Editor, Anatomical Pathology
David Driman graduated from the University of Cape Town and completed residency training in anatomical pathology at the University of Toronto. Following fellowship training in gastrointestinal pathology, he joined the University of Western Ontario (UWO), where he is now professor of pathology and a staff pathologist at London Health Sciences Centre. Between 1998 and 2007, Dr. Driman served as residency program director for both anatomical pathology and general pathology at UWO, and he has received several teaching awards for both undergraduate and postgraduate medical education.

Todd F. Hatchette, BSc, MD, FRCPC
Section Editor, Medical Microbiology
Todd Hatchette obtained his medical degree from Memorial University. He is currently a medical microbiol-
ogist and infectious disease consultant at the Queen Elizabeth II Health Sciences Centre and Capital District Health Authority in Halifax, where he has been director of the Virology and Immunology Laboratory since 2004. He is an associate professor in the Department of Pathology at Dalhousie University and has published extensively on influenza, mumps, and Q-fever. Dr. Hatchette is a member of the National Pandemic Coordinating Committee.

Michael J. Shkrum, MD, FRCPC
Section Editor, Forensic Pathology

Michael Shkrum is a staff pathologist at London Health Sciences Centre and a professor in the Department of Pathology at the University of Western Ontario. He began his practice in 1985 in London following a forensic pathology fellowship in North Carolina. Currently, he is the director of the Southwestern Ontario Forensic Pathology Unit. Dr. Shkrum coauthored a text titled *Forensic Pathology of Trauma – Common Problems for the Pathologist* and is a co-principal investigator with the University of Western Ontario Multidisciplinary Accident Research Team.

Louis D. Wadsworth, MB ChB, FRCPH, FRCPC
Section Editor, Hematopathology

After medical school at the University of Manchester, Louis Wadsworth trained in hematopathology in the United Kingdom. He is currently a hematopathologist at the Children’s and Women’s Health Centre of British Columbia, a clinical professor in the Department of Pathology at the University of British Columbia, and a member of the Department of Paediatrics. His major interest is in transfusion medicine, and he is a member of the National Advisory Committee for Blood and Blood Products. In 2006, Dr. Wadsworth received the William Boyd Award of the Canadian Association of Pathologists.
Cotyledonoid Dissecting Leiomyoma of the Uterus (Sternberg Tumour): A Clinicopathological Study of Six Cases

Anil Misir, MD, FRCPC, Dean Daya, MD, MHA, FRCPC, FASCP, Monalisa Sur, MBBS, FCPath, MMed, FRCPat, FRCPat, FRCPC

ABSTRACT
Cotyledonoid dissecting leiomyoma of the uterus (CDL) is a rare variant of the uterine leiomyoma first described in 1975. Twenty-nine cases of this tumour, ranging in size from 6.0 to 41.0 cm, have been previously published in the English literature. The age range of these patients was 23–73 years, with a mean of 43 years. In this series, we present six additional cases collected over a 5-year period (1997–2001).

Grossly, CDLs may be confused with a sarcoma because of its infiltrative growth pattern. However, cytologically they are benign with no mitoses, nuclear atypia, or coagulative necrosis. The combination of these gross and cytological features is quite distinctive but may confuse the uninitiated. Clinically, CDL behaves similarly to classic leiomyomas. In summary, CDL is a rare, benign smooth muscle tumour. It is important to be aware of this entity to avoid overly aggressive treatment.

RÉSUMÉ
Le léiomyome cotylédonoïde disséquant (LCD) de l’utérus est une variante rare du fibromyome décrit pour la première fois en 1975. Vingt-neuf cas de cette tumeur, dont la taille variait de 6 à 41 cm, ont déjà été publiés dans la documentation anglaise. La fourchette d’âge de ces patientes était de 23 à 73 ans et l’âge moyen, de 43 ans. Cette série présente six autres cas recueillis sur une période de cinq ans (entre 1997 et 2001).

À l’échelle macroscopique, il est possible de confondre le LCD avec le sarcome en raison de son profil de prolifération. Toutefois, l’examen cytologique montre qu’il est bénin, car il ne présente aucune activité mitotique, atypie nucléaire ou nécrose de coagulation. La combinaison de ces particularités macroscopiques et cytologiques permet de le distinguer, mais peut dérouter le non-initié. Sur le plan clinique, le LCD se comporte de la même façon que le léiomyome classique. En résumé, le LCD est une tumeur bénigne rare du muscle lisse. Il est important de connaître cette entité pour éviter d’entreprendre un traitement trop agressif.
Cotyledonoid dissecting leiomyoma (CDL) is a rare variant of leiomyoma. Originally described in 1975 by David et al. as “grape-like leiomyoma,” CDL was given its present designation in 1996 by Roth et al., who also gave it the eponym Sternberg tumour. Thus far, 29 cases have been reported in the English-language literature. We present an additional six cases. Clinically, CDLs most often occur in women of reproductive age (mean age 43 years, range 23–73 years) with non-specific clinical presentations. Treatment is typically total abdominal hysterectomy with bilateral salpingo-oophorectomy. In the existing literature, there are no cases of recurrence. One previously published case had incomplete excision, but no recurrence was detected.

The most characteristic trait of CDL is the distinctive combination of a malignant gross appearance with a benign histology and clinical behaviour. It is important to be aware of this entity to prevent overly aggressive treatment for this benign smooth muscle neoplasm.

Materials and Methods
The cases for this series were collected over a 5-year period (1997–2001). Gross pictures along with hematoxylin and eosin slides were reviewed. Immunohistochemical stains for smooth muscle actin (SMA), muscle actin (HHF-35), desmin, and vimentin were selectively performed using the standard labelled streptavidin biotin (LSAB) technique.

Results
Clinical Details
Patient age ranged from 35 to 57 years (mean 46). Presenting symptoms included menorrhagia, abdominal pain, and pelvic mass. One case had extensive tumour burden with ascites, pleural effusion, and omental nodules. A second case involved a mass adherent to the urinary bladder wall (Table 1).

Total abdominal hysterectomy was the treatment in all the cases, with three patients also undergoing unilateral or bilateral salpingectomy with or without oophorectomy. No local recurrence or distant metastasis was seen in five cases. One patient underwent omentectomy to remove omental nodules; she presented with recurrence in the omentum due to inadequate resection of the omental nodules at the time of treatment. As of June 2007, all patients were alive and well (follow-up period of 6–10 years).

Pathological Features
Grossly, the cases were exophytic with a “cotyledonoid” (seed-lobe-like subdivisions resembling discoid placenta)

<table>
<thead>
<tr>
<th>Source</th>
<th>Age</th>
<th>Presentation</th>
<th>Location of Tumour</th>
<th>Size (cm)</th>
<th>Intrauterine Dissecting Component</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td>Present</td>
<td>TAH</td>
<td>NED 10 y</td>
</tr>
<tr>
<td>Case 2</td>
<td>35</td>
<td>Fibroid uterus</td>
<td>NA</td>
<td>6</td>
<td>Present</td>
<td>TAH</td>
<td>NED 10 y</td>
</tr>
<tr>
<td>Case 3</td>
<td>42</td>
<td>Abdominal , swelling, ascites, plural effusion</td>
<td>NA; omental nodules present</td>
<td>30</td>
<td>Present</td>
<td>TAH-BSO, omentectomy, appendectomy</td>
<td>Recurrence of nodules, alive and well 9 y</td>
</tr>
<tr>
<td>Case 4</td>
<td>41</td>
<td>Mass adherent to bladder</td>
<td>Right uterine wall, right broad ligament</td>
<td>22</td>
<td>Present</td>
<td>TAH, left SO</td>
<td>NED 10 y</td>
</tr>
<tr>
<td>Case 5</td>
<td>44</td>
<td>Irregular menses, enlarged uterus</td>
<td>Bilateral, lower third of corpus</td>
<td>16</td>
<td>Present</td>
<td>TAH, left oophorectomy</td>
<td>NED 6 y</td>
</tr>
<tr>
<td>Case 6</td>
<td>57</td>
<td>Multilobed uterus, menorrhagia</td>
<td>Posterior wall, extending to LUS</td>
<td>5.5</td>
<td>Present</td>
<td>TAH</td>
<td>NED 8 y</td>
</tr>
</tbody>
</table>

BSO = bilateral salpingo-oophorectomy; LUS = lower uterine segment; NA = not available; NED = no evidence of disease; SO = salpingo-oophorectomy; TAH = total abdominal hysterectomy; TH, total hysterectomy.
extrauterine component present on the serosal surface of the uterus with extensions into broad ligament (Figure 1). One case showed small pale nodules in the omentum. The “dissecting” intramural component showed multiple well-defined nodules extending into normal myometrium with continuity between myometrial tumour and serosa.

Microscopically, the intramural and extrauterine nodules were composed of spindle cells arranged in disorganized, swirling fascicles showing a sinuous dissecting growth pattern between normal myometrial smooth muscle bundles (Figures 2 and 3). The interface showed hydropic connective tissue with ectatic and congested vessels. Two cases showed epithelioid morphology. Hyalinization and hydropic degeneration were seen in five cases.

Intravascular component, mitoses, necrosis, and nuclear pleomorphism were not identified (Figure 4). One case demonstrated nodules of benign-appearing tumour cells within the omentum (Figure 5).

All tumours were immunohistochemically positive for SMA, HHF-35, desmin, and vimentin.

Discussion

CDL is a rare variant of the most common uterine neoplasm. The first published report of this tumour was authored by David et al. in 1975 under the designation “grape-like leiomyoma.” In 1996, Roth et al. published a series of four archival cases dating from the mid-1940s and coined the current name as well as the eponym “Sternberg tumour.”

Excluding this series, 29 cases of this tumour have been published in the English-language literature (Table 2). Tumours have ranged in size from 6.0 to 41.0 cm. CDLs tend to be unilateral, arising from the cornu and growing into the broad ligament. The age range in the published literature is 23–73 years, with most patients in the reproductive age group. The lesion has also occurred in pregnancy, resulting in clinical symptoms. In all previously published cases where follow-up is known, there was no evidence of recurrence after the initial surgery. In one case of incomplete excision, there was no subsequent increase in size. Similar tumours have also been found in the esophagus.

Grossly, CDLs appear exophytic and resemble placental tissue (“cotyledonoid,” resembling a seed lobe). They are present in the myometrium and may extend into the adnexa and omentum grossly. Cytologically, however, they are benign with no mitoses, nuclear atypia, or coagulative necrosis. The combination of these gross and cytological
<table>
<thead>
<tr>
<th>Year</th>
<th>Source</th>
<th>Age</th>
<th>Presentation</th>
<th>Location of Tumour</th>
<th>Size (cm)</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>David et al.</td>
<td>65</td>
<td>Vaginal discharge and bleeding, abdominal tenderness</td>
<td>Fundus of uterus, adhering to the peritoneal surface of bladder and penetrating the cervix</td>
<td>15</td>
<td>TH</td>
<td>NA</td>
</tr>
<tr>
<td>1980</td>
<td>Payan et al.</td>
<td>34</td>
<td>Persistent menorrhagia</td>
<td>Fundus of uterus bulging into the peritoneal cavity</td>
<td>10</td>
<td>TH</td>
<td>NED 3.5 y</td>
</tr>
<tr>
<td>1995</td>
<td>Brand et al.</td>
<td>24</td>
<td>Lower abdominal swelling</td>
<td>Fundus of uterus, retroperitoneal space, and peritoneal cavity</td>
<td>NA (&gt;1.6 kg)</td>
<td>Incomplete resection with postoperative progestogen therapy</td>
<td>Residual tumour with no increase in size after 15 mo</td>
</tr>
<tr>
<td>1996</td>
<td>Roth et al.</td>
<td>39</td>
<td>Right pelvic mass</td>
<td>Cornu of uterus, broad ligament, and invading into the pelvic cavity</td>
<td>10.3</td>
<td>TAH-BSO</td>
<td>NED 26 mo</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td>41</td>
<td>Uterine bleeding, enlarged uterus</td>
<td>Cornu of uterus, broad ligament, and projecting into the pelvic cavity</td>
<td>10</td>
<td>TH</td>
<td>NED 41 y</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td>23</td>
<td>Uterine bleeding, pelvic mass</td>
<td>Cornu of uterus, broad ligament, and projecting into the pelvic cavity</td>
<td>25</td>
<td>Resection of tumour</td>
<td>NED 16 y</td>
</tr>
<tr>
<td>1998</td>
<td>Fukunaga and Ushigome</td>
<td>35</td>
<td>Abdominal pain, vaginal bleeding</td>
<td>Fundus and lateral wall</td>
<td>18</td>
<td>TAH, left SO</td>
<td>NED 6 mo</td>
</tr>
<tr>
<td>1999</td>
<td>Menolascino-Bratta et al.</td>
<td>26</td>
<td>Uterine mass found at evaluation of acute appendicitis</td>
<td>Multicentric growth, including both fallopian tubes, broad ligaments, and peritoneum</td>
<td>16</td>
<td>TAH-BSO</td>
<td>NA</td>
</tr>
<tr>
<td>2000</td>
<td>Roth and Reed</td>
<td>46</td>
<td>Pelvic mass</td>
<td>Fundus of uterus, left broad ligament, and pelvic cavity</td>
<td>34</td>
<td>TAH-BSO, omental biopsy</td>
<td>NED 1 mo</td>
</tr>
<tr>
<td>2002</td>
<td>Cheuk et al.</td>
<td>55</td>
<td>Menorrhagia and uterine prolapse</td>
<td>Right posterior wall of uterus, broad ligament, and pelvic cavity</td>
<td>10</td>
<td>TAH-BSO</td>
<td>NED 14 mo</td>
</tr>
<tr>
<td>2002</td>
<td>Kim et al.</td>
<td>26</td>
<td>Incidental during pregnancy evaluation</td>
<td>Posterior uterine wall, left broad ligament, and pelvic cavity</td>
<td>12</td>
<td>Resection</td>
<td>NED 2 y</td>
</tr>
</tbody>
</table>
Table 2. Review of English-Language Literature: Clinicopathological Features

<table>
<thead>
<tr>
<th>Year</th>
<th>Source</th>
<th>Age</th>
<th>Presentation</th>
<th>Location of Tumour</th>
<th>Size (cm)</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Jordan et al.⁷</td>
<td>46</td>
<td>Right adnexal mass</td>
<td>Uterus and right broad ligament</td>
<td>22</td>
<td>TAH-BSO</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46</td>
<td>Weight gain, central abdominal pain, and pelvic mass</td>
<td>Uterus and right broad ligament</td>
<td>20</td>
<td>TAH-BSO</td>
<td>NED 5 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46</td>
<td>Pelvic mass</td>
<td>Uterus and right broad ligament</td>
<td>10</td>
<td>TAH and right broad ligament mass removal</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46</td>
<td>Pelvic mass</td>
<td>Uterus and bilateral broad ligaments</td>
<td>18</td>
<td>TAH</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>Menorrhagia, large fibroid uterus</td>
<td>Uterus and bilateral broad ligaments</td>
<td>13</td>
<td>STH</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>Uterine mass and infertility</td>
<td>Uterus and left broad ligament</td>
<td>18</td>
<td>Resection</td>
<td>NA</td>
</tr>
<tr>
<td>2003</td>
<td>Stewart et al.⁹⁹⁹</td>
<td>58</td>
<td>Abdominopelvic mass</td>
<td>Fundus</td>
<td>16.4</td>
<td>TAH-BSO</td>
<td>NA</td>
</tr>
<tr>
<td>2005</td>
<td>Gurbuz et al.²⁰</td>
<td>67</td>
<td>Persistent ovarian cyst</td>
<td>Left isthmic region, broad ligament</td>
<td>10</td>
<td>TAH-BSO</td>
<td>NED 8 mo</td>
</tr>
<tr>
<td>2006</td>
<td>Maimoon et al.⁵</td>
<td>40</td>
<td>Urinary retention</td>
<td>Lower uterus</td>
<td>NA</td>
<td>TAH, unilateral salpingo-oophorectomy</td>
<td>NA</td>
</tr>
<tr>
<td>2006</td>
<td>Saeed et al.⁹</td>
<td>27</td>
<td>Pelvic mass</td>
<td>Posterior wall, left broad ligament</td>
<td>41</td>
<td>TAH-BSO</td>
<td>NED 1 mo</td>
</tr>
<tr>
<td>2007</td>
<td>Mathew et al.¹¹</td>
<td>Early 30s</td>
<td>Abdominal distension and discomfort</td>
<td>Left lateral uterine corpus</td>
<td>30</td>
<td>Myomectomy</td>
<td>NA</td>
</tr>
<tr>
<td>2007</td>
<td>Shelekhova et al.¹⁰</td>
<td>73</td>
<td>NA</td>
<td>Fundus</td>
<td>8</td>
<td>TAH</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Palpable abdominal mass, pain</td>
<td>Fundus, cornua, broad ligament</td>
<td>9</td>
<td>TAH-BSO</td>
<td>NED 2 y</td>
</tr>
<tr>
<td>2007</td>
<td>Weissferdt et al.⁸</td>
<td>52</td>
<td>Menorrhagia, abdominal pain, tiredness</td>
<td>Left broad ligament</td>
<td>6</td>
<td>TAH, right SO</td>
<td>NED 18 mo</td>
</tr>
<tr>
<td>2009</td>
<td>Driss et al.⁶</td>
<td>47</td>
<td>Vaginal bleeding</td>
<td>Lower uterus</td>
<td>NA</td>
<td>TAH-BSO</td>
<td>NA</td>
</tr>
<tr>
<td>2009</td>
<td>Raga et al.¹⁵</td>
<td>33</td>
<td>Menorrhagia, abdominal pain</td>
<td>Right lateral aspect of corpus</td>
<td>6</td>
<td>Myomectomy</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available; NED = no evidence of disease; SO = salpingo-oophorectomy; STH = subtotal hysterectomy; TAH-BSO = total hysterectomy bilateral salpingo-oophorectomy; TH = total hysterectomy.
Source: Adapted from Saeed et al.,⁹ with additional cases.
features is quite distinctive but may lead the inexperienced pathologist or surgeon to confuse this entity with sarcoma, particularly on the gross specimen, thus leading to overtreatment.4–6

Ultrastructurally, CDL demonstrates benign features. It is composed of cells that are similar to normal smooth muscle cells, showing a characteristic folded nucleus. The cytoplasm contains intermediate filaments and microfilaments with focal densities. There are also abundant collagen fibrils in the matrix.10 On flow cytometry, CDL shows deoxyribonucleic acid diploidy with a relatively low S-phase fraction (5.6%), consistent with a benign nature.14

However, on magnetic resonance imaging, the appearance is that of an irregular mass.15

It is instructive to think of separate gross and microscopic differential diagnoses for this lesion. Grossly, CDL resembles a leiomyosarcoma or other sarcoma. Indeed, there have been instances where excessively radical surgery was performed for this reason.4–6 Microscopically, however, the lesion lacks nuclear atypia, mitoses, and coagulative necrosis. The benign histology might suggest other variants of leiomyoma (Table 3). However, the unique combination of a malignant gross appearance with a benign cytology makes the diagnosis clear.

Table 3: Differential Diagnosis of CDL

<table>
<thead>
<tr>
<th>Entity</th>
<th>Feature(s) Distinguishing Entity from CDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrating leiomyoma including leiomyomatosis</td>
<td>Infiltrating margins; not grossly cotyledonoid</td>
</tr>
<tr>
<td>Disseminated peritoneal leiomyomatosis</td>
<td>Numerous small (&lt;2 cm) nodules</td>
</tr>
<tr>
<td>Benign metastasizing leiomyoma</td>
<td>Morphologically benign leiomyoma at distant site (lungs, lymph nodes, etc.)</td>
</tr>
<tr>
<td>Parasitic leiomyoma</td>
<td>“Detached” leiomyoma present in the pelvis with blood supply derived from the omentum</td>
</tr>
<tr>
<td>Leiomyoma with vascular intrusion</td>
<td>Grossly normal leiomyoma with microscopic vascular invasion noted</td>
</tr>
<tr>
<td>Intravascular leiomyomatosis</td>
<td>Grossly visible invasion of histologically benign smooth muscle invading into vascular structures; and/or microscopic extension of smooth muscle into vascular spaces outside the confines of a leiomyoma</td>
</tr>
</tbody>
</table>

CDL = cotyledonoid dissecting leiomyoma.
In summary, CDL is a rare, benign smooth muscle tumour. Owing to the unusual gross appearance, the diagnosis of a malignant lesion may be considered; however, CDL lacks nuclear atypia, mitotic activity, and coagulative tumour necrosis. It is important to be aware of this entity to avoid overly aggressive treatment.

Acknowledgements
We would like to acknowledge the following physicians who generously contributed cases to this series: cases 2 and 4 – Drs. Ian Beavon and Wayne Grayson, Department of Pathology, South African Institute of Medical Research, University of Witwatersrand, Johannesburg, South Africa; and case 3 – Dr. Dhiren Govender, Department of Pathology, University of Natal, Durban, South Africa.

References
The five-step microskills model of clinical teaching, also known as the one-minute preceptor (OMP) model, was first described in the family medicine literature by Neher and colleagues in 1992. It was originally designed for use by faculty to enhance the teacher-student interaction in busy ambulatory teaching encounters. Over the past 17 years, it has become a popular method for improving teaching skills in both faculty and residents of clinically based programs such as family medicine and internal medicine. In this brief article, the application of the OMP model to nonclinical programs such as pathology is explored.

The Model
The five microskills are as follows:

1. Get a commitment – the preceptor asks the learner for a diagnosis
2. Probe for evidence – the preceptor uses more direct questioning to evaluate the learner’s knowledge base or reasoning skills
3. Teach general rules – the preceptor teaches the learner “take-home points” resulting from the case, preferably based on an area of weakness identified in the learner
4. Reinforce what was done well – the preceptor provides positive feedback
5. Correct mistakes – the preceptor provides constructive feedback

The Evidence
Aagaard et al. compared the OMP model with the traditional model of preceptorship (Table 1) and found that clinical teachers using the OMP model were equally or better able to diagnose correctly patients’ medical problems and felt more confident in rating their students’ abilities. They also rated the OMP encounter as more effec-
tive and efficient than the traditional model.
Irby et al.\(^3\) found that preceptors using the OMP model were more likely to teach about the disease and disease processes, whereas those using the traditional model focused on generic skills such as history taking and presentation. The authors suggest that the OMP model reveals more of the thinking of the learner and thus shifts teaching toward higher-order, disease-specific points rather than general processes.
Salerno et al.\(^4\) demonstrated that preceptors using the OMP model provided more feedback and feedback that was more likely to be specific. Preceptors using the OMP model reported that teaching encounters were more successful and they were better able to evaluate learners and create plans for self-directed learning.
Furney et al.\(^5\) found that the OMP model was effective for providing improvements in residents’ teaching skills. Residents employing the OMP model reported significant improvements in giving feedback, which is one of the most challenging problems in clinical education. On the measure of resident satisfaction of the model, 87% rated the model as “useful or very useful.” A similar study\(^6\) found that the OMP model improved both residents’ teaching skills and attitudes toward teaching.
In summary, the available evidence suggests that the OMP model is easy to use, efficient, and effective. It enhances the ability of preceptors to evaluate learners and improves self-directed learning. When employing this model, preceptor feedback improves in both quality and quantity.

The Pathology Setting
Teaching is a fundamental part of a pathologist’s clinical practice. In the academic setting, pathologists are responsible for educating medical students, residents from both pathology and other clinical disciplines, and other physicians. For most academic pathologists, the majority of their teaching time is spent at the microscope with pathology residents. A recent report outlined innovative teaching methods in pathology,\(^7\) but to my knowledge there have not been any published reports detailing the challenges that pathologists face when they are teaching their craft to junior learners.
A review of teaching and learning in ambulatory care found inadequacies of teaching in these settings that can be at least partly attributed to unpredictability, variability, and lack of time.\(^8\) Teaching in the pathology setting appears to face the same challenges, although there is no objective evidence to support this claim. It could be argued that a lack of time for teaching and balancing service with educational responsibilities are significant barriers to effective teacher-learner interactions in pathology. The OMP model, which has been shown to be as time efficient as the traditional model,\(^2\) should offer the same improvements to teaching in the pathology setting and is worth further exploration. Table 2 outlines a case scenario that illustrates how the OMP model can be used to enhance a teaching encounter at the microscope.

Conclusions
The OMP model is a practical teaching tool that has gained acceptance in clinical medicine. It has been shown to improve the teaching process without prolonging it. Teaching in pathology faces similar challenges to teaching in the ambulatory setting, with time constraints being the most apparent. Because pathologists spend a great deal of their time teaching, it follows that the introduction of more effective teaching strategies would be welcome. The OMP model may prove to be an easy-to-use teaching tool that can be used in the pathology setting and should be explored. In addition, further studies into the challenges of teaching in pathology are required as this seems to be

<table>
<thead>
<tr>
<th>Microskill</th>
<th>Example of Question/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Get a commitment</td>
<td>“What do you think the diagnosis is?”</td>
</tr>
<tr>
<td>2. Probe for evidence</td>
<td>“What are the features that support this diagnosis?” or “What other entities did you consider and why?”</td>
</tr>
<tr>
<td>3. Teach general rules</td>
<td>“When I look at biopsies from this site, my approach is ...”</td>
</tr>
<tr>
<td>4. Reinforce what was done well</td>
<td>“You did a good job considering the clinical history when arriving at this diagnosis.”</td>
</tr>
<tr>
<td>5. Correct mistakes</td>
<td>“The next time you come across this type of biopsy, don’t forget to consider entities that are easily treated.”</td>
</tr>
</tbody>
</table>
an area that has been neglected in both medical education and pathology literature.

Acknowledgements
I thank Dr. Ken Newell for his assistance with the preparation of this manuscript.

References

Massive Lymphocytic Infiltration in a Uterine Leiomyoma Post-Gonadotropin-Releasing Hormone Agonist Treatment

Desiree H. Skeete, DM (Path), Robert H. Riddell, MD, Wendy L. Wolfman, MD, Terence J. Colgan, MD

ABSTRACT
Massive lymphocytic infiltration of uterine leiomyomas is exceptionally rare. There are occasional reports in the English literature, and five cases were associated with preoperative gonadotropin-releasing hormone (GnRH) agonist therapy. In this article, we report a case of uterine leiomyoma with massive lymphocytic infiltration (ULMLI) in a woman treated with a GnRH agonist. The relevant clinicopathological data were obtained from medical records. A 38-year-old woman who was diagnosed with a uterine leiomyoma underwent a subtotal hysterectomy after receiving preoperative treatment with a GnRH agonist. Microscopically, the leiomyoma displayed the characteristic features, hyaline necrosis and marked inflammatory cell infiltration by predominantly small mature lymphocytes. The infiltrate was confined to the leiomyoma, and immunophenotyping revealed a mixed composition of lymphocytes. The findings were those of ULMLI. With the increasing use of GnRH agonists, pathologists should be aware of this
Although uterine leiomyomas are common, massive lymphocytic infiltration of these neoplasms is exceptionally rare. This finding was initially described in 1989, with occasional reports documented subsequently. The pathogenesis is unknown, and there are no clearly identifiable risk factors. However, a few cases have been associated with preoperative gonadotropin-releasing hormone (GnRH) agonist therapy. GnRH agonists are used in the medical and preoperative management of uterine leiomyomas. These drugs cause pituitary desensitization to GnRH and a consequent decreased production of follicle-stimulating hormone and luteinizing hormone, resulting in decreased ovarian estrogen production. This hypoestrogenic state simulates menopause and causes a temporary reduction in the size of estrogen-dependent tissues. On cessation of GnRH agonist therapy, estrogen receptors are upregulated and leiomyomas quickly retain their original size. The GnRH agonist–induced size reduction of the leiomyomas contributes to decreased intraoperative blood loss and facilitates alternative surgical approaches.

We report another case of uterine leiomyoma with massive lymphocytic infiltration (ULMLI) associated with GnRH agonist use, and highlight morphological mimics.
focally, but there was no evidence of vasculitis. Marked leukocytic infiltration by primarily small, mature lymphocytes (Figures 1 and 2), occasional reactive follicles, scattered plasma cells, histiocytes, mast cells, and rare eosinophils was evident. The infiltrate was confined to the leiomyoma. Immunophenotyping demonstrated positivity for B- (CD20) and T- (CD3, CD4, and CD8) lymphocytic, plasmacytic (CD79a), mast cell (CD117), and histiocytic (CD68) markers. T cells were predominant, with CD8+ cells the major subset.

Discussion
There are 10 reports discussing 20 cases of UMLI in the English literature. The clinical features are similar to those seen with uterine leiomyomas in general, and grossly there are no distinctive macroscopic appearances. The histological hallmark is patchy or diffuse marked infiltration of the leiomyoma by predominantly small, mature lymphocytes. Lymphoid follicles and other mononuclear leukocytes may be scattered throughout. Rare granulocytes also may be present. No immature myeloid or monocytic precursors are present. The infiltrate is confined to the leiomyoma. Immunophenotyping may be necessary to establish the mixed composition of the infiltrate and exclude a lymphoma. There is positivity for various B- and T-cell, plasmacytic, histiocytic, and mast cell markers, as in this case. Most of the lymphocytes are of the cytotoxic (CD8+) type. An analysis of surface immunoglobulin expression, if performed, shows results in keeping with a polyclonal infiltrate. The main diagnostic dilemma is the misinterpretation of UMLI as a lymphoma involving the uterus. Other differential diagnoses include uterine pyomyoma and inflammatory pseudotumour, and all are rare diagnoses.

Primary uterine lymphomas are usually of cervical origin and the diffuse large B-cell subtype. Involvement of the corpus occurs mainly in widely disseminated lymphomas. Grossly, lymphomas show a diffuse, tan to white fleshy appearance in the corpus. In addition, nodular infiltrates may be evident. Leiomyomas with superimposed infiltration by lymphoma are softer than those with UMLI. Lymphomas show a diffuse, dense infiltration of atypical, usually large lymphoid cells in the myometrium and the leiomyoma, in contrast to UMLI in which the mixed inflammatory infiltrate is composed of mature leukocytes with mainly small, mature lymphocytes. The confinement of the infiltrate to the leiomyoma is an important characteristic to distinguish UMLI from uterine involvement by lymphoma. Immunohistochemistry is invaluable in

Figure 1. Diffuse infiltration of the leiomyoma by predominantly small, mature lymphocytes (centre and left). Note the absence of lymphocytic infiltrate in adjacent myometrium (right). (Hematoxylin and eosin; original magnification 200×)

Figure 2. Lymphocytic infiltrate within leiomyoma. (Hematoxylin and eosin; original magnification 600×)
establishing the diagnosis of lymphoma. The results of immunophenotyping highlight the B- or T-cell lineage of the neoplastic cells, with the exact immunoprofile depending on the type of lymphoma present. The commonest type of lymphoma seen in the uterus, the diffuse large B-cell subtype, in itself a heterogeneous entity, has a variable immunophenotype.

Inflammatory pseudotumours are well-circumscribed, bosselated masses with a homogeneous, focally trabeculated, white-tan cut surface. Unlike leiomyomas, inflammatory pseudotumours lack a whorled appearance. Histologically, there is a myofibroblastic spindle-cell proliferation usually arranged in interdigitating fascicles with variable collagenization and a prominent mixed inflammatory infiltrate consisting of numerous plasma cells, neutrophils, lymphocytes, and histiocytes. Other inflammatory cells such as eosinophils and mast cells may be seen rarely. The inflammatory infiltrate extends into the surrounding myometrium in places, in contrast to ULMLI. The presence of abundant neutrophils is also an important discriminatory factor. In inflammatory pseudotumours, collagen production varies from inconspicuous to dense hyaline bands. The latter, because of their resemblance to hyalinization seen in leiomyomas, may contribute to diagnostic confusion, and more so in patients who received preoperative GnRH agonist therapy. Since the introduction of antibiotics, most pyomyomas occur in the postpartum setting and are accompanied by sepsis. When leiomyomas with hydropic, cystic, and edematous degenerative changes become infected, they may also present as pyomyomas. Grossly, cystic leiomyomas containing purulent exudate and necrotic material are evident. Microscopically, pyomyomas, unlike ULMLI, display marked acute suppurative inflammation, with variable extension into the myometrium. There was a history of preoperative GnRH agonist therapy in five of the 20 reported patients with ULMLI. Some studies that investigated the effects of GnRH agonist therapy on leiomyomas have described minimal lymphocytic infiltration. One noted marked quantities of chronic inflammatory cells, especially lymphocytes, in some leiomyomas, compared with controls. The morphological changes in leiomyomas in patients treated with GnRH agonists are variable and include altered cellularity and increased hyaline necrosis but no significant increase in mitotic activity or cytological atypia. The leiomyomas with massive lymphocytic infiltration in patients treated with GnRH agonists showed no increased mitotic activity in four cases, myocyte degeneration in three, endothelial cell hyperplasia/prominence in two, and destructive arteritis in one.

The mechanism of any association between GnRH agonist therapy and ULMLI has not been elucidated. One pathogenetic hypothesis is of an autoimmune mechanism leading to a direct cytotoxic effect. Our case is the first report of ULMLI in a patient with an autoimmune illness, raising the question of whether the cessation of GnRH agonist results in an upregulation of epitopes that might result in an autoimmune process. Graves’ disease has a T-cell predominant infiltrate, similar to ULMLI, and is linked to polymorphisms in the cytokotic T-lymphocyte-associated-4 (CTLA-4) gene. The CTLA-4 receptor inhibits T-cell responses to self-antigens.

With the increasing use of GnRH agonists in the management of uterine leiomyomas, pathologists should be aware of this unusual reaction of massive lymphocytic infiltrates within uterine leiomyomas and the features that distinguish it from the main differential diagnoses.

References
In the fall of 2008, a brief notice in the Canadian Association of Pathologists Newsletter drew attention to an article in CAP Today that expressed concern over the future of ophthalmic pathology in the United States. Traditionally in the United States, eye pathology laboratories have been situated physically and “intellectually” in departments of ophthalmology, which have often subsidized both the laboratory and the ophthalmic pathologist. A similar situation existed in Canada until 1987, when anatomical pathologists with subspecialty training in ophthalmic pathology began to be appointed in some academic centres. Since that time, ophthalmic pathology has become largely the preserve of pathologists and pathology departments in this country, as it has been in the United Kingdom for over 50 years. The United States is now moving more in that direction. There are two major disadvantages associated with this change. Given the caseload of most surgical pathology laboratories, the ophthalmic pathologist in a pathology department may have inadequate time to devote to the discipline. Furthermore, the concentration on diagnostic pathology necessitated by that caseload may lead to a neg-

Canadian Association of Pathologists
William Boyd Lecture 2009

Ocular pathobiology: lessons for diagnostic pathology

J. Godfrey Heathcote, MA, MB BChir, PhD, FRCPC

ABSTRACT
This lecture reviews the knowledge of ophthalmic pathology at the time of William Boyd (1929) and emphasizes the importance of understanding ocular biology to diagnostic ophthalmic pathology. The structure of the Descemet’s/endothelial complex is described in the context of corneal disease. The information to be gained from the examination of eyes removed at autopsy is discussed, and a simple approach to the cytopathology of ocular fluids is presented.

RÉSUMÉ
Cet exposé passe en revue les connaissances en matière de pathologie ophthalmique à l’époque de William Boyd (vers la fin des années 1920) et souligne l’importance d’une bonne compréhension de la biologie oculaire dans la pathologie ophthalmique de diagnostic. La structure du complexe endothélium/membrane de Descemet est décrite dans le contexte des maladies de la cornée. On y expose les renseignements qu’on peut tirer de l’examen d’yeux prélevés à l’autopsie et une approche simple de la cytopathologie des liquides oculaires.

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Competing interests: Godfrey Heathcote is the editor-in-chief of Canadian Journal of Pathology. He is an editor of Garner & Klintworth’s Pathobiology of Ocular Disease, 3rd edition (2008), and has received royalties from the Taylor & Francis Publishing group.

This article was peer reviewed.
lect of the underlying pathobiology of ocular disease. As Jakobiec pointed out in the CAP Today article, there is a “real danger the knowledge that doesn’t make it into textbooks will be lost.” It is because of this second reason that I chose the subject of this lecture: to emphasize that in ophthalmic pathology, perhaps more than in some other subspecialties of anatomical pathology, a knowledge of pathobiology is of great value in the diagnostic arena.

However, this is a lecture to commemorate a distinguished Canadian pathologist of an earlier generation, and it is therefore appropriate to begin with an appreciation of the state of ophthalmic pathology in William Boyd’s time and his understanding of it. To do that, I need to go back 80 years to 1929 and examine three textbooks that were in use at that period.

In 1929, the second edition of William Boyd’s textbook Surgical Pathology was published. Although Boyd used drawings of a corneal wound to illustrate the mechanisms of healing in the section on general pathology, the section on surgical pathology did not contain a chapter on the eye. The index included only five ophthalmic diseases:

- Eye in secondary syphilis
- Eye in congenital syphilis
- Xanthelasma
- Graves’ disease (but with no mention of the orbitopathy)
- Retinoblastoma of the brain (sic)

Five years earlier, in 1924, Robert Muir, the professor of pathology at Glasgow University, had published the first edition of his Text-Book of Pathology, which has been used by subsequent generations of Anglophone medical students who have attended medical school outside North America. Not only was there no chapter on the pathology of the eye in that edition, the word eye did not appear in the index. The only ocular lesions that did appear in the index were the following:

- Albuminuric retinitis
- Argyll Robertson phenomenon
- Exophthalmic goitre (but again without mention of the orbitopathy)
- Xanthelasma

Even the discussion of congenital syphilis did not mention the interstitial keratitis.

One might be forgiven for thinking that in 1929 little was known, and less was cared, about ophthalmic pathology. Nothing could be further from the truth. That year also saw the publication of The Pathology of the Eye by Jonas Friedenwald, the pathologist of the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. Not surprisingly perhaps, Friedenwald, like Muir and Boyd, devoted considerable attention to syphilis, albuminuric retinitis, and retinoblastoma, but what is noteworthy about this volume is the deliberate concentration on the pathobiology of ocular diseases. On the first page, Friedenwald wrote: “It is not the purpose of this book to present in any complete sense the special pathology of the eye. The aim is rather to form a bridge leading from general pathology to this special field so that the student will not find himself lost in a maze of seemingly strange and unrelated facts.”

Two pages later, Friedenwald acknowledged the importance of the eye as a biological system, the investigation of which had led to fundamental discoveries in embryology, biophysics, and protein biochemistry, as well as pathology: “In the history of the development of pathology the eye occupies a notable position. Much of the early work on inflammation by Cohnheim, and others, was accomplished through experimentation on the eye. The absence of blood vessels in the cornea, for instance, made it possible to differentiate the cellular from the vascular factors in inflammation, and the transparency of the cornea, on the other hand, made it possible to study early lesions in the living tissue.”

There are many statements in, and omissions from, Friedenwald’s book that we would consider surprising in the light of modern knowledge and practice. For example, there is no mention of sebaceous carcinoma, and malignant melanoma of the choroid merits only a few pages. Although he does note that metastatic tumours to the eye are most frequently found within the choroid, he does not explain why. Detailed studies of the incidence of metastases in different target organs and its relationship to blood flow came much later.

Over the past 80 years, the fundamental pathobiology underlying many of these lesions and processes has become apparent. In the course of this lecture, I want to review a few of these insights and highlight some of the features that can inform the general anatomical pathologist as well as the specialist in ophthalmic pathology. There is a tradition in ophthalmic pathology that micro-
scopic description of the eye begins with the anterior segment of the eye, and it is to the cornea that I first turn.

**Pathobiology of the Descemet’s/Endothelial Complex**

In 1929 Friedenwald wrote, “The cornea is lined on its inner surface by a tough, glassy, elastic membrane (Descemet’s membrane), the exact nature and significance of which is very imperfectly known. It resembles in its physical properties and histological staining reactions the equally poorly understood membrane which forms the capsule of the lens … There appear to be no structures analogous to these membranes elsewhere in the human body.”

There are, in fact, numerous analogous structures throughout the body, and pathologists examine them every day. Descemet’s membrane and the lens capsule are just unusually thick and structurally complex basement membranes, and much of the knowledge of the biochemical structure and biosynthesis of basement membranes has been derived from study of these two examples.

The lens capsule has a lamellar substructure that can be interpreted as units of basal lamina stacked upon each other. Like all basement membranes, it is composed of cross-linked type IV collagen but also contains heparan sulphate proteoglycan. The capsule thickens with age by the accretion of additional lamellae, and the lamellar arrangement renders it susceptible to tangential splitting. This may occur with aging or uveitis but is particularly associated with thermal injury and was a recognized occupational hazard of industrial glass blowers.

Descemet’s membrane is deposited on the posterior surface of the corneal stroma from the 12th week of gestation by a layer of endothelial cells of neural crest origin (Figure 1). The principal function of this Descemet’s/endothelial complex is to keep the cornea dehydrated by means of an ion pump in the cells, although the basement membrane also provides great mechanical strength. It is resistant to penetration by leukocytes and tumour cells but can be penetrated by fungi, in particular *Fusarium*. It also has elastic properties and stains with elastic stains, yet does not contain elastic fibres.

This strength and elasticity is demonstrable when the corneal stroma is damaged by alkali or a fulminating corneal infection. Under these circumstances, the collagenous stroma is gradually degraded until the integrity of the eyeball is preserved only by Descemet’s membrane, which stretches into a thin, bulging membrane (descemetocele). This stretching would be consistent with a lamellar organization, and the morphological basis of this was demonstrated by the ultrastructural studies of Jakus. In tangential sections of bovine Descemet’s membrane, she demonstrated a hexagonal array of nodes and filaments (Figure 2), which in perpendicular sections appeared to be stacked on top of each other and give a banded pattern of 110 nm periodicity in perpendicular sections.
appearance with a periodicity of 110–120 nm. This hexagonal lattice is composed of collagen type VIII and contains the tetra-functional cross-links desmosine and isodesmosine that characterize insoluble elastin and are presumably responsible for its strength and resistance to proteolytic digestion (Heathcote and Bruns, unpublished).8

The morphology of human Descemet’s membrane is more complex in that the hexagonal lattice is only seen in the basement membrane deposited prenatally; after birth, non-banded filamentous material, principally collagen type IV, is gradually added throughout life.8 Thus, human Descemet’s membrane is composed of an anterior banded zone (ABZ) and a non-striated, non-lamellar posterior non-banded zone (PNBZ). If, however, the endothelium is injured, it responds by adding a third layer of extracellular matrix on the internal aspect of the basement membrane, which is called a posterior collagenous layer (PCL).10 These three growth phases thus provide “a historical record of the fetal and post-natal function of the endothelium.”11 Alterations in the thickness and organization of these three zones give an indication of when an endothelial disturbance began. For example, in congenital posterior polymorphous dystrophy of the cornea, characterized by severe corneal clouding in the first few months of life, the ABZ is quite abnormal, indicative of an abnormality occurring prenatally.12

Is this of any use in diagnostic pathology? One of the commonest indications for corneal transplantation is Fuchs’ endothelial dystrophy, a gradual decompensation of the cornea accompanied by edema and a pronounced thickening of Descemet’s membrane. This thickening may be lamellar and uniform or it may manifest as guttate excrescences on the posterior surface, or a combination of the two. Although the presence of guttatae is characteristic of this dystrophy, it is not pathognomonic since they may be seen in other conditions such as macular corneal dystrophy and congenital syphilis. Whatever the light microscopic appearance of Descemet’s membrane, ultrastructural examination reveals a characteristic change in that the PNBZ is <4 µm thick, the thickness expected at about the age of 20 years. In other words, the endothelial dysfunction that may manifest clinically at the age of 80 years has in reality started to develop at the age of 20 years. The different light microscopic appearances of Descemet’s membrane in this condition reflect different forms of PCL.10 Another common indication for corneal transplantation is pseudophakic bullous keratopathy: corneal edema from endothelial disturbance as a result of the insertion of an intraocular lens. Such lenses may be implanted in eyes with unrecognized Fuchs’ dystrophy, increasing the likelihood of corneal decompensation and transplantation. In the corneal specimens removed at grafting, the presence of an underlying Fuchs’ dystrophy can be identified by light microscopy and confirmed, if necessary, by electron microscopy.

It was mentioned above that Descemet’s membrane may stretch and become thin, forming a descemetocele, if the anterior support of the stroma is lost through infection or injury. In other circumstances, Descemet’s membrane simply breaks and the free ends curl up. This may be seen in acute corneal hydrops in keratoconus and in congenital glaucoma where there is a reactive deposition of basement membrane to form giant scrolls of Descemet’s membrane in which the free end can be readily identified.13 Why such a clean fracture should occur in a basement membrane that is strong and elastic remains unclear.

It is interesting to note that corneal surgeons are developing a variety of surgical techniques for the management of Fuchs’ dystrophy that do not involve the transplantation of the whole cornea but, rather, the Descemet’s/endothelial complex. Specimens from these procedures are now being received in ophthalmic pathology laboratories.

The “Autopsy Eye”

The question sometimes arises as to whether eyes should be removed at autopsy. Since the eye is a discrete, readily accessible organ that often shows manifestations of systemic and neurological diseases, it could be argued that removal for pathological examination should be routine. However, unless general pathologists were willing to participate, the substantial increase in workload for eye pathologists and their technologists would be insupportable and the overall value would be uncertain. Nevertheless, the examination of eyes removed at autopsy may contribute to the diagnosis and to our understanding of disease in selected circumstances:

- Evaluation of systemic and neurological diseases, such as diabetes mellitus and multiple sclerosis
- Evaluation of perinatal death and congenital malformations
- Evaluation of accidental death under circumstances where visual impairment may have been a factor
- Evaluation of specific ocular diseases, particularly those of the retina
With regard to this last circumstance, Lee has written, “Many ocular diseases evolve slowly and rarely terminate with enucleation. If enucleation is required, the end-stage pathology and the effects of treatment totally obscure the primary abnormality, particularly so in those which end with retinal detachment. Careful scrutiny of autopsy eyes will provide useful documentation of the peripheral retinal diseases which predispose to detachment.”

One example where the examination of the eye at autopsy is useful relates to accidental death in the elderly. At the autopsy of an 83-year-old woman who was found one morning dead at the bottom of her basement steps, there was no indication of either a cardiac or cerebral event. There was, however, a history of poor peripheral vision, and the pathologist removed the eyes for examination. The macroscopic appearance was typical of a disciform scar associated with age-related macular degeneration (ARMD), and this was confirmed by microscopy when a fibrovascular scar was seen beneath degenerate neurosensory retina in the region of the macula. It is reasonable to conclude that the lady had little or no central vision and may not have been aware of the stairs in the dark.

In Western countries, the prevalence of ARMD increases from 0.2% in the 50- to 59-year age group to 16.4% in those over 80 years. Although a specific cause has not been established, familial aggregation and twin studies indicate a genetic contribution, and several predisposing factors have been identified, particularly chronic exposure to visible light and cigarette smoking. There are two major clinical types of ARMD; the atrophic or “dry” type and the exudative or “wet” type. The former accounts for 80–90% of ARMD, and visual impairment, although progressive, is usually moderate. Although less prevalent, wet ARMD causes 90% of the cases of blindness, and severe visual loss may occur rapidly. Both forms are thought to reflect a disturbance in the function of the neurosensory retina and the retinal pigment epithelium (RPE). This is manifested initially as a deposit of granular, periodic acid–Schiff (PAS)-positive material beneath the RPE on the inner surface of Bruch's membrane, a thick connective tissue layer that supports the RPE and has a central lamina of elastin (Figure 3). In early studies, this material was referred to as basal linear deposit, although the terminology has since become rather complicated and basal laminar deposit is now more frequently used. It appears to be derived from the basal portion of the RPE cells and may serve as a chemo-attractant for macrophages and other inflammatory cells. Its presence at the interface between the RPE and the choroidal capillaries may also disturb the balance of nutrients and biochemical messengers in this region and predispose to further RPE damage. In those cases where a neovascular membrane forms beneath the RPE, the new blood vessels arise from the choroidal capillaries and extend through defects in Bruch's membrane. Although it was initially assumed that inflammatory cells might create these defects, recent research into the remodelling of elastic fibres in adult tissues has suggested that abnormalities in lysyl oxidase–like 1 protein (LOXL1) may contribute to the fragmentation of Bruch’s membrane. LOXL1 deficiency has been implicated in abnormalities of elastic tissue, and atrophic changes in the female genital tract and may help explain why early menopause is linked to ARMD.

It is not generally appreciated that these early studies,
which gave us our first glimpse of the pathogenesis of ARMD and 40 years later have led to targeted therapy in the form of anti-vascular endothelial growth factor (VEGF) antibodies, were based on a post-mortem study. In the 1970s, Sarks, an Australian ophthalmologist, documented at regular intervals the clinical appearance of the eyes in a group of 216 patients admitted to a hospital in Sydney for long-term care. She later carried out a histopathological examination of 378 eyes obtained post-mortem from these patients and identified the importance of the basal linear deposit in ARMD: “The formation of this basal linear deposit beneath the macula proved the most reliable histological criterion of the stage of the disease and correlated most closely with the clinical findings.”  

19

The changes with age in the amount of basal linear deposit and its association with retinal pathology are indicated in Table 1. The formation of a disc-shaped (disciform) fibrovascular scar beneath the macula is easily recognizable on pathological examination, and a ribbon of basal linear deposit may be identified within the scar (Figure 4). Hyperplasia of RPE cells may result in pigmentation of the scar and, in the past, eyes were occasionally enucleated because of an incorrect clinical diagnosis of choroidal melanoma.

At the other extreme of life, there are good reasons for pathological examination of the eyes from deceased infants, particularly those with congenital anomalies. The size of the eye and its histological appearance are strong indicators of gestational age in normal fetuses and premature neonates. Figures have been published that allow a reasonable estimate of age from the anteroposterior (sagittal) dimension of the globe and the dimensions of the cornea. 24 Since the eye is a small organ with a very precise anatomical arrangement of its component tissues, it has proved ideal for morphogenetic studies, and the stages of prenatal human ocular development have been well documented. 25 There are several easily recognizable, and hence useful, histological features in the developing eye that may assist the pathologist in the determination of the gestational age of a fetus. Retinal folds are frequently present in the eyes of infants and should not be interpreted as pathological or evidence of trauma without an appropriate clinical history.

Although the prevalence of many congenital anomalies is declining in Canada, they are still implicated in 24% of neonatal deaths. 26,27 Pathological examination of the eye is needed for a complete perinatal autopsy, can provide useful information, and may help to distinguish syndromic from sporadic anomalies. Ocular anomalies are frequently associated with orofacial clefts and abnormalities of the urinary tract and are prominent features of the three major trisomies, 13, 18, and 21. 28 The molecular genetic abnormalities underlying many of these anomalies are slowly being defined.

**Cytopathology of Ocular Fluids**

It is not unusual for a cytopathology laboratory to receive specimens from the two discrete fluids contained in the normal eye: the aqueous humour in the anterior chamber and the vitreous humour in the posterior chamber. When intraocular pathology, typically a break in the neurosensory retina, results in retinal detachment, subretinal fluid accumulates beneath the neurosensory retina, and this fluid may occasionally be sent to the laboratory for cytopathological assessment. Although screening for, and diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean Age (y)</th>
<th>BLD</th>
<th>Visual Acuity*</th>
<th>CNV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>67.5</td>
<td>Absent</td>
<td>6/6</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>75.3</td>
<td>Patchy</td>
<td>6/9</td>
<td>0</td>
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<tr>
<td>III</td>
<td>81.9</td>
<td>Thin continuous</td>
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<tr>
<td>IV</td>
<td>84.0</td>
<td>Thick continuous</td>
<td>6/24</td>
<td>14</td>
</tr>
<tr>
<td>V</td>
<td>85.6</td>
<td>With loss of pigment in RPE</td>
<td>3/60</td>
<td>42</td>
</tr>
<tr>
<td>VI</td>
<td>81.9</td>
<td>Within scar</td>
<td>&lt;3/60</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 1. Progressive Deposition of Basal Linear Deposit in ARMD**

ARMD = age-related macular degeneration; BLD = basal linear deposit; CNV = choroidal neovascularization; RPE = retinal pigment epithelium.

*Most commonly recorded visual acuity.

Source: Based on Sarks. 19
of, malignancy is the primary use of cytopathology, it should be remembered that intraocular tumours are not common and the fluid may be sent to the laboratory as much to gain insight into the pathological process within the eye as to exclude malignancy.

Aqueous Humour

Diagnostic aqueous paracentesis is used largely under two circumstances: when inflammatory cells accumulate in the inferior angle of the anterior chamber to form a hypopyon, and when a visible pathological change occurs in the surface of iris and the distinction between neoplasm and inflammation has to be made. The value is illustrated by the case of a 66-year-old woman who presented with a gradual decrease in visual acuity and soreness in one eye, accompanied by an elevation of intraocular pressure. The iris was noted to look abnormal with a lump inferiorly. Three laser iridotomies produced a transient reduction in intraocular pressure, but inflammation persisted. After 2 months, the pupil was irregular and unreactive and a fine membrane was noted on the temporal iris with a nodule at 4 o’clock (Figure 5). An aspirate of the anterior chamber yielded clusters of cytokeratin-positive epithelial cells, consistent with metastatic carcinoma, and a computed tomography scan of the chest revealed a lung nodule. The patient opted for enucleation of the eye, and pathological examination confirmed metastatic adenocarcinoma. Although only 13.3% of intraocular metastases are found in the anterior segment, approximately half of these seed along the anterior surface of the iris. These metastases often present with an inflammatory picture, possibly reflecting tumour necrosis, and it is not unusual in the case of bronchial carcinoma for ocular symptoms to develop before the existence of the primary is recognized.

Vitreous Humour

Vitreous fluid may be submitted to the laboratory as a result of a diagnostic needle aspiration or from a pars plana vitrectomy (PPV), a procedure frequently performed by vitreo-retinal surgeons for both diagnostic and therapeutic purposes. In most ophthalmic centres, specimens from PPV are not routinely submitted for cytopathological examination; but this can be useful, particularly in cases of persistent intraocular inflammation or suspected intraocular malignancy. An early study of PPV undertaken for diagnostic purposes in chronic uveitis suggested that a definitive diagnosis could be rendered in 46% of cases.

The normal vitreous contains few cells, and the presence of occasional lymphocytes and small histiocytes in a specimen from a therapeutic PPV would not be regarded as abnormal. In chronic uveitis, lymphocytes and histiocytes may spread into the vitreous humour. Their numbers may be quite low, and often cytopathological examination offers nothing more than confirmation that there is indeed an inflammatory infiltrate. Anything unusual
about the infiltrate, such as pronounced hypercellularity, a neutrophilic component, the presence of granulomas, or the presence of apoptotic cells, calls for clinicopathological correlation.\textsuperscript{31,32} Primary intraocular lymphoma arises within the neurosensory retina, and both viable and dying cells are readily shed into the vitreous. The background debris is a strong clue to the diagnosis. Systemic lymphoma that has spread to the eye is principally located within the uveal tract but can still release neoplastic cells into the vitreous.

The eye is prone to a variety of infections, and, even in the modern era of cataract surgery, the possibility of postoperative endophthalmitis remains a worry for both patient and surgeon. PPV has a major role in the management of endophthalmitis, in terms of the removal of causative organisms and inflammatory mediators, the removal of vitreous membranes allowing a better distribution of antibiotics, and the provision of diagnostic material for both microbiology and cytopathology. Although acute postoperative endophthalmitis may be caused by virulent microorganisms, such as \textit{Staphylococcus aureus} and \textit{Streptococcus pneumoniae}, a low-grade endophthalmitis following cataract surgery may be caused by the gram-positive bacillus \textit{Propionibacterium acnes}, which proliferates within the lens capsule and incites a granulomatous inflammatory response. Vitreous cytopathology may be of help in identifying this bacterium (Figure 6). Endogenous fungal endophthalmitis may occur in the immunosuppressed, and also has an insidious onset. The diagnosis can be difficult to make and, again, vitreous cytopathology may have a role. Fungal endophthalmitis is mostly caused by \textit{Candida} spp. or \textit{Aspergillus} spp. and occurs in about 10% of patients with systemic fungal infections.\textsuperscript{33}

\section*{Subretinal Fluid}

Subretinal fluid accumulates when a tear in the neurosensory retina leads to detachment from the underlying retinal pigment epithelium. Since this form of retinal detachment (rhegmatogenous) can be successfully repaired, enucleation specimens are only received in the pathology laboratory if reattachment is unsuccessful and the eye later becomes blind, painful, and unsightly. There have been few studies of the cellular composition of subretinal fluid, although the question has been raised as to whether this could in some way influence, and perhaps predict, the likelihood of success in reattachment surgery. Those studies that have been performed indicate that the cellularity of the fluid is quite variable and independent of the dura-
tion of detachment. RPE cells predominate in detachments of less than 3 weeks’ duration, and experimental studies suggest that early proliferation of RPE cells is part of the reparative process (Figure 7A). They lose their pigment rapidly and may undergo spindle-cell metaplasia, perhaps a precursor to the formation of an epiretinal membrane. In subretinal fluid from detachments of longer duration (>4 weeks), macrophages predominate (Figure 7B). Their function is likely to be clearance of the debris that accumulates in response to the degeneration of the photoreceptors. Other inflammatory cells, such as lymphocytes and neutrophils, may be present, as may erythrocytes. Intact photoreceptor cells may also be seen in the fluid (Figure 7C).

The presence of photoreceptor elements in the subretinal fluid may have clinical significance. Retinal detachment usually results in a reduction of intraocular pressure as the secretion of aqueous humour by the ciliary epithelium shuts down. Occasionally, particularly with tears in
the peripheral retina, there is a transient increase in intraocular pressure that may return to normal when the retina is reattached (Schwartz’s syndrome). Examination of the aqueous humour by electron microscopy in cases of this syndrome has shown the presence of intact and degenerate photoreceptor outer segments, and intracameral injection of rod outer segments can cause an experimental type of Schwartz’s syndrome.44

Conclusion
In this lecture, I have tried to give you a taste of some aspects of ocular pathobiology that have interested me over the past 35 years. Like others in the small community of ophthalmic pathologists, I have found the appeal of ocular pathology to lie in its intriguing blend of clinical ophthalmology, basic science, and diagnostic anatomical pathology. In many disciplines, our clinical colleagues have realized that, in order to understand the diseases they treat, they have to “follow the biology” and are now pursuing what would once have been regarded as pathological research. We too must continue to observe nature’s experiments with a critical eye and not neglect the underlying biology.

References
1. Lusky K. The eyes don’t have it – facing a shortfall in ophthalmic pathology. CAP Today 2008;September.
Report Sets the Stage for Molecular Oncology and Genetic Testing across Ontario

Today, science allows us to examine a person’s genetic makeup and use this information to predict risk for some cancers, give a diagnosis of cancer, and determine how a patient will respond to treatment, thus allowing for targeted therapies. This breakthrough field, called molecular oncology, has evolved rapidly. To ensure that Ontarians have access to these services, and the health system can meet demand, the Molecular Oncology Task Force, sponsored by Cancer Care Ontario (CCO), released its report and recommendations on January 26, 2009.

This is a key initiative of the 2008–2011 Ontario Cancer Plan and a first step in ensuring Ontarians have access to high-quality genetic testing. Advances in this field allow us to test a person for predisposition to cancer and for treatment to be tailored to a patient’s cancer. It is imperative that our health system keep pace with these developments by making these tests available in a safe and sustainable manner.

Ontario has a strong licensing and quality assurance program in place for most types of testing. However, the system has not kept pace with rapid advances in genetics and molecular testing.

Immediate action is required on the part of all stakeholders in the system to ensure access, quality, accountability, and sustainability, to strengthen quality and safety, and to prepare the system for the future. The recommendations put forth by the task force are intended for testing in public hospital laboratories being considered for public funding. These recommendations include the following:

- Assigning an oversight body responsible for a test approval process that evaluates clinical validity and utility, ensuring cost-effectiveness, implementing new technologies when evidence warrants, and delivering discoveries to patients quickly
- Ensuring quality and patient safety by implementing a mandatory approval process for each genetic test performed by laboratories in Ontario for routine patient care, including accreditation and licensing of laboratories and appropriate credentialing of personnel
- Educating providers and patients about molecular oncology testing and related clinical genetic services
- Developing a sustainable system for funding of cancer tests and clinical genetic services so that Ontarians have equal access to high-quality tests and targeted therapies that can be of great benefit to patients and cost-effective for the system

By working together to facilitate the above recommendations, government, Quality Management Program – Laboratory Services (QMP-LS), researchers, CCO, training organizations, and the clinicians and scientists providing genetic services will ensure a stronger, sustainable, safe, and cost-effective system of molecular oncology services for Ontario.

For more information and to see the full report visit www.cancercare.on.ca.

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Head, Laboratory Genetics and Molecular Diagnostics
The University Health Network, Toronto, Ontario

Response

We would like to thank the Cancer Care Ontario (CCO) Molecular Oncology Task Force for their report detailing their recommendations for the regulation of the expanding world of molecular diagnostics. This is a thoughtful review of the current state of molecular testing and evaluation of ways to ensure that testing is performed at the highest possible quality. While we agree with many of the suggestions put forward by the task force, there are some recommendations that concern us.

The task force recommends the creation of a provincial body to oversee test approval, delisting of obsolete tests, funding, licensing, accreditation, credentialing, quality assurance, and location of services (recommendation 1 in the report). We support the creation of such a body, as well as the suggestion that this body has funding that will be distributed to the appropriate sites for approved tests. As stated within the report, molecular genetics is a new class of tests at the Ministry of Health and Long-Term Care and should now be part of the mandate of Quality Management Program – Laboratory Services (QMP-LS). QMP-LS is familiar with laboratory operations and quality assurance and has established a program for laboratory accreditation (Ontario Laboratory Accreditation) that should be expanded to include assessment of molecular diagnostics. The creation of an additional provincial body
Recommendations for the Implementation

Health Canada, in its report to the director takes away from the major issues, which are to ensure the quality of the test performed and that an MD is acceptable if the individual has the appropriate training.

The recommendation regarding participation of molecular laboratories in external proficiency testing programs (Recommendation 3) is fully supported, and we too believe it should be examined as part of the laboratory accreditation process.

Recommendations 4 and 6, informing providers and patients about services and promoting translational research to implement new tests and technologies, are beyond the role of diagnostic molecular laboratories but are important initiatives that CCO should consider. Any provincial funding body for diagnostic molecular testing should be aware of ongoing translational research so that it can support the decision to migrate new tests into a diagnostic setting. There should however be a clear separation between the funding and operations of diagnostic as opposed to research molecular tests.

The task force recommends that funding be tied to quality and utilization (Recommendation 5). Following on the previous comments, we would support that funding for molecular diagnostics be tied to laboratories that participate in QMP-LS and/or recommended quality assurance programs. We also strongly support the criterion that only laboratories performing sufficient numbers of tests will be approved to provide this service. The linkage of competence to caseload done is well accepted, for example, with Her2/neu testing. It is not clear who will define what constitutes “sufficient testing,” and this needs to be established for the recommendation to be practical.

Rita Kandel, MD, FRCP(C), Chief
Aaron Pollett, MD, FRCP(C), Staff Pathologist
Dept. of Pathology and Laboratory Medicine
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Response

Cancer Care Ontario’s Molecular Oncology Task Force was convened to provide recommendations aimed at ensuring that the Ontario system can meet the increasing demands for molecular oncology testing and clinical cancer genetics services, while ensuring quality and safety for patients, and adequate preparation and vision to capitalize on this rapidly advancing field of knowledge.

The oversight body envisioned by the task force is advisory in nature. It is intended to work in conjunction with existing structures and processes, rather than replacing or
duplicating them. The wording of the recommendation was deliberate. It states that the body will “oversee system planning for these services.” The task force felt strongly that there is a need to provide a focus on genetic services in oncological diseases, an area of genetics that is currently underdeveloped provincially. The system oversight described in the report involves ensuring experts in molecular oncology conduct proactive scanning of the science and use this information, along with cancer surveillance data, to advise on system capacity issues. The recommendation went on to say that this body would advise key stakeholders on test approval, delisting, funding, licensing, and other important issues. It did not intend that this new body duplicate successful efforts already in place in other organizations. Rather, it recommended that MDs and PhDs with oncology expertise come together to support other organizations by providing oncology-specific advice. QMP-LS participated in the development of the task force recommendations, and the report acknowledges their critical ongoing role in quality assurance and accreditation.

The task force’s recommendations relating to accreditation and credentialing were intended to promote patient safety by ensuring that laboratories conducting tests and reporting molecular, genetic, and cytogenetic results meet minimum standards both technically and professionally. This recommendation is not meant to be exclusionary but, rather, to ensure that there are quality guidelines in place throughout the province. Whereas there is a very valuable role for research in the development and optimal application of biomarkers, genomic knowledge, and genetic tests, it must be clear what credentials and accreditation laboratories need if the data are to be used in patient management.

With respect to credentials of laboratory directors, the task force was careful in choosing the language for its recommendation stating, “CCMG or ABMG or equivalent should be considered.” Task force members did not intend to exclude MDs from being laboratory directors but, rather, to ensure that directors have appropriate experience in laboratory genetics and genetic test interpretation. The intent was to highlight the fact that this complex area of laboratory medicine requires specialized knowledge similar to that seen in other fields of medicine. The importance of MD involvement in service provision was acknowledged by the task force. We agree that the focus should be on the quality of the test performed and that the important issue is appropriate training regardless of whether the individual has an MD or PhD.

We appreciate Drs. Kandel and Pollett’s endorsement of the task force recommendations relating to external proficiency testing, information-sharing, tying funding to quality criteria, and translational research. We agree that there should be a separation between the funding and operations of clinical and research testing. We believe there is a need to define quality criteria such as minimum volumes using an open, transparent, and evidence- and consensus-based process. This is something CCO would be pleased to facilitate.

We are pleased that some of the issues raised in the report have already been addressed, such as changes to laboratory licensing to include genetics as a new class of test. We await a response from government regarding the remaining recommendations. In the interim, we are examining which recommendations can be implemented within existing resources.

Carol Sawka, MD, FRCPC
Vice-president, Clinical Programs and Quality Initiatives
Cancer Care Ontario
Suzanne Kamel-Reid, PhD, FACMG
Chair, Molecular Oncology Task Force

Can CJP Help with Pathology Staffing?
I read with interest the article “Pathology Training in Canada: A Perspective from Two Senior Residents” [Can J Pathol 2009;1:43], in which the authors express worry about insufficient Canadian positions for new pathology graduates.

We have in New Brunswick nine unfilled AP/GP positions (23% of the total). In Edmundston, one pathologist fills three positions; in Fredericton, four fill six positions; in our hospital, there are three filling five positions. We are all slowly burning out, calling for help, but the CV pile is empty. Ironically, the page facing the article advertises another vacancy in NB.

New Brunswick is not unique. The authors are probably right about the lack of opportunities in Toronto and other large cities, but young pathologists must know that there are plenty of vacant positions in smaller centres throughout Canada. Letting them know is, however, a challenge. How can laboratory directors in non-teaching hospitals reach residents? I would love to see a centralized database of positions and candidates for the whole of Canada; is there already one? If not, could this new journal and/or the CAP-ACP website play this role?

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Secretary, NB Association of Laboratory Physicians
General/Anatomical and Haematological Pathologists

Regional Health Authority B (RHA B) is dedicated to providing quality client-centered care to a population of 600,000 within the province of New Brunswick in addition to communities in Prince Edward Island and northern Nova Scotia. RHA B encompasses the following areas: Fredericton, Miramichi, Moncton, Upper River Valley, and Saint John.

RHA B invites applications for full time positions located at the Saint John Regional Hospital and The Moncton Hospital.

Saint John:  
The Saint John Regional Hospital has 23 areas of specialty medicine and surgery, and is supported by a vast array of research, education, health promotion activities and community partnerships. In the near future, the Dalhousie New Brunswick Medical Education Program will be based on the adjacent property to the Saint John Regional Hospital at the University of New Brunswick, Saint John campus.

Saint John is a thriving industrial center situated at the mouths of the Saint John and Kennebecasis Rivers on the scenic Bay of Fundy. Recreational opportunities include easy access to picturesque inland waterways, sailing, skiing, golf, etc. The City also boasts excellent educational and cultural facilities, including a campus of the University of New Brunswick, which offers a wide variety of undergraduate and postgraduate programs. Visit the city’s website at www.cityofstjohn.com.

- **Anatomical/General Pathologist**  
  (Training or experience in Dermatopathology would be an asset)  
  As part of a team of staff pathologists, the successful applicant will be expected to participate in all aspects of the pathology service. Involvement in autopsy service would be desirable. Participation in teaching of medical students and residents is expected, and collaborative or individual research is encouraged. Candidates must be an MD eligible for New Brunswick licensure plus FRCP or equivalent higher qualification in the specialty of anatomical or general pathology.

- **Anatomical/Forensic Pathology**  
  As part of a team of staff pathologists, the successful applicant will be expected to participate in all aspects of the pathology service. Participation in teaching of medical students and residents is expected, and collaborative or individual research is encouraged. Candidates must be an MD eligible for New Brunswick licensure plus FRCP or equivalent higher qualification in the specialty of anatomical pathology or general pathology. Additional training or experience or certification in Forensic Autopsy is highly desirable.

- **Anatomical Pathologist**  
  (Training or experience in Renal pathology would be an asset)  
  As part of a team of staff pathologists, the successful applicant will be expected to participate in all aspects of the surgical and autopsy pathology service. Participation in teaching of medical students and residents is expected, and collaborative or individual research is encouraged. Candidates must be an MD eligible for New Brunswick licensure plus FRCP or equivalent higher qualification in the specialty of anatomical or general pathology.

Moncton:  
The Moncton Hospital is a 365-bed critical care and major referral hospital that offers services in Trauma, Neurosurgery, Burns, Oncology, Infectious Diseases, Neonatal Care, Provincial Child and Adolescent Psychiatry and Vascular Surgery plus extensive services in elevated secondary and primary care. The Moncton Hospital is one of the largest single employers within metro Moncton. The Moncton Hospital offers excellent opportunities for teaching, clinical research and academic affiliation with Dalhousie University.

Moncton is the fastest growing city in Atlantic Canada. Embracing the motto “Resurge”, Moncton has redefined itself time and time again through years of dynamic change and growth. We truly are a community, and a hospital, on the move. The city, with adjoining municipalities has a population of more than 135,000 and has been ranked as one of the best Canadian cities for quality of community life. There is an abundance of educational, cultural and recreational opportunities including easy access to warm water beaches of the Northumberland Strait and also the scenic Bay of Fundy area. Visit the City’s website at www.moncton.ca.

- **General/Anatomical Pathologist**  
  Permanent position available for a successful candidate to join a congenial group of laboratory physicians, consisting of five anatomical and general pathologists, a medical biochemist, two haematopathologists, and a microbiologist. We have a full spectrum of anatomic pathology, cytology and haematopathology in addition to a very active service in chemistry and microbiology in a dynamic laboratory accredited by the College of American Pathologists since 1987. The laboratory will move to a new facility in Fall of 2009, located near the surgical suites and intensive care units, and with much new equipment. There is a potential for a departmental directorship on rotational basis for an individual with administrative experience or interest. Haematopathology or cytopathology experience would be an asset.

The Department of Pathology and Laboratory Medicine requires one of the following qualifications: a) certification or Fellowship in Pathology of the Royal College of Physicians and Surgeons of Canada, or eligibility to write the examination for Fellowship in Pathology; b) certification by the American Board of Pathology; c) certification by the College des médecins du Québec; d) membership of the Royal College of Pathologists of England and Ireland. The salary range is determined by the New Brunswick Medical Pay Plan, depending on qualification and experience.

Please send applications and CV to:  
Dr. David Kogon, Chief of Staff/Medical Director, Moncton, NB  
Telephone: (506) 857-5532  
Fax: (506) 857-5545  
E-mail: medstaff@serha.ca
The Division of Hematopathology in the Department of Pathology & Laboratory Medicine of Capital Health in Halifax, Nova Scotia, requires a full-time Hematopathologist at the QEII Health Sciences Centre. This facility is a large, tertiary care teaching hospital affiliated with Dalhousie University and is the major referral centre for the Maritime Provinces. The successful applicant will join an active team of seven Hematopathologists and one clinical scientist that serve a wide variety of adult patient programs including Hematology, Oncology, bleeding disorders, bone marrow and organ transplantation. The Division of Hematopathology has an active Royal College residency training program. It is a busy clinical service, providing state of the art diagnostic approaches and research opportunities in morphology, molecular pathology, bone marrow transplantation, coagulation disorders, blood transfusion, flow cytometry and HLA typing. This permanent position requires a commitment to clinical service, teaching and research. The successful applicant will be expected to participate in most aspects of Hematopathology service with a focus on any of the areas of flow cytometry and molecular pathology. A protected time for research activities could also be arranged for an appropriate candidate.

Applicants must hold a Canadian certification (or acceptable equivalent) in Hematological Pathology. The successful candidate will hold a faculty appointment in the Department of Pathology at Dalhousie University.

Halifax, the capital city of Nova Scotia, has a metropolitan population of approximately 400,000. The city has a very good public school system, five universities and colleges and a number of cultural facilities.

In accordance with Canadian Immigration requirements, all qualified candidates are encouraged to apply; however, Canadian and permanent residents will be given priority.

Potential candidates are invited to apply by forwarding a letter of interest and CV before December 31, 2009 to:

Dr. Irene Sadek,
Head, Division of Hematopathology,
Room 204 Mackenzie Bldg,
5788 University Avenue,
Halifax, NS, Canada B3H 1V8
Email: irene.sadek@cdha.nshealth.ca
The Opportunity
The Department is a unified department that combines the academic, research, and service components within Saskatoon Health Region and the University of Saskatchewan College of Medicine. The Department of Pathology and Laboratory Medicine has an accredited residency training program in General Pathology and is involved in the training of undergraduates, graduate students, and post-doctoral fellows. The Department’s broad range of clinical programs includes subspecialty aspects of pathology that are well suited for educational and research activities. The Department includes the division of Anatomical Pathology (including Histology and Cytopathology), Medical Biochemistry, Hematopathology, Microbiology, Virology, Tissue Typing, Cytogenetics, Inherited Metabolic Diseases, Diagnostic Molecular Pathology, and Transfusion Medicine.

The Division of Anatomical Pathology serves a population base of approximately 500,000 and has a staff of 15 staff pathologists, including specialists in neuro- and renal pathology. The hematopathology division has a staff of four. The top of the current salary scale is $293,000 (Gri) and is under review. As employees, the pathologists enjoy a generous vacation and benefits package.

Canadian Light Source (CLS) Synchrotron
The $173.5 million CLS synchrotron, a national facility owned by the University of Saskatchewan, is the largest science project in Canada in more than 50 years. This facility is a unique national resource that will light the way to a new era of science and innovation for academic, industrial, and governmental researchers. An active Anatomy and Cell Biology CLS Users Group is available for collaborative research with clinical faculty.

The University
A publicly funded institution established in 1907, the University of Saskatchewan offers a full range of curricula, both academic and professional, with students registered in 13 colleges, including health sciences and veterinary sciences. The College of Medicine has an intake of 84 students per year with a commensurate number of positions for residency training. This intake will soon increase to 100.

Saskatoon Health Region (SHR)
SHR is one of the most integrated and complex health delivery agencies in Canada and is the largest health region in Saskatchewan, serving more than 360,000 residents in over 100 cities, towns, and rural municipalities. Saskatoon Health Region is the largest single employer in the province with over 12,000 staff and 800 physicians. The city’s three hospitals — St. Paul’s, City, and Royal University — comprise three of the province’s tertiary teaching centres.

The City
Saskatoon Shines — with more hours of sunshine than any other major Canadian city. With a population of 250,000, Saskatoon is the largest city in Saskatchewan, boasting small town spirit and big city amenities. World class events, festivals, and attractions... a strong arts and music focus... a short drive to northern lake country... a variety of indoor and outdoor sporting facilities... and more golf courses per capita than anywhere in North America. The city is noted for its outstanding walking and biking trails along the riverbank and excellent education facilities, including the University of Saskatchewan. What’s more — everything is within 15 minutes of home. Saskatoon is easily accessible by major airlines.

To Apply:
If you are seeking a challenging career opportunity, please apply in confidence by October 15, 2009:
Jackie McKee
Medical Affairs
Saskatoon Health Region
Saskatoon City Hospital
2nd Floor, Administration
701 Queen Street
Saskatoon, Saskatchewan S7K 0M7
Phone: (306) 655-7948
Fax: (306) 655-7951
E-mail: jackie.mckee@saskatoonhealthregion.ca
5 postes vacants en pathologie

HÔPITAL RÉGIONAL DR-GEORGES-L.-DUMONT,
MONCTON, NOUVEAU-BRUNSWICK
Le département de pathologie, qui compte 3 anatomo-pathologistes, est à la recherche de 2 pathologistes soit : 1 en anatomo-pathologie et 1 en hémato-pathologie
La langue de travail est le français.
Faire parvenir votre curriculum vitae à Francine Thibodeau, Hôpital régional Dr-Georges-L.-Dumont, 330, avenue Université, Moncton, NB E1C 2Z3. Téléphone : (506) 862-4230, courriel : francinet@rrsb.nb.ca

HÔPITAL RÉGIONAL D’EDMUNDSTON,
EDMUNDSTON, NOUVEAU-BRUNSWICK
Le département de pathologie, qui compte 1 pathologiste, est à la recherche de 2 pathologistes certifiés en anatomo et en pathologie clinique
Faire parvenir votre curriculum vitae au Bureau du directeur médical, Hôpital régional d’Edmundston, 275 boul. Hébert, Edmundston, NB E3V 2S8. Téléphone : (506)739-2385

HÔPITAL RÉGIONAL CHALEUR,
BATHURST, NOUVEAU-BRUNSWICK
Le département de pathologie, qui compte 4 pathologistes, est à la recherche d’un (1) pathologiste avec certification en anatomo-pathologie et en pathologie clinique avec intérêt/certification en hématologie et/ou dermatologie.
Faire parvenir votre curriculum vitae à Evelyne Valotaire – Agente de recrutement, Hôpital régional Chaleur, 1750 Prom. Sunset, Bathurst NB E2A 4L7. Téléphone: (506) 544-3784, courriel : evelyne.valotaire@rsrha.ca

Informations supplémentaires
Les candidats choisis doivent être agréés soit par le CRMCC, le CMQ, l’American Board of Pathology ou par un autre organisme reconnu par le Collège des médecins et chirurgiens du N.-B.

La rémunération est basée sur le Plan de rémunération du personnel médical du N.B. À partir du 1 avril 2009 – 231 994 $ à 256 393 $ et à partir du 1 avril 2010 – 255, 194 $ à 282,032 $
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Email: hospitalservices@gamma-dynacare.com