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About the Cover

This image shows characteristic nuclear features of papillary thyroid carcinoma with the oval nuclei, fine chromatin, nuclear grooves, micronucleoli, and intranuclear inclusions.

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Among the reminiscences of past presidents of the Canadian Association of Pathologists (CAP–ACP) published in the first issue of this journal, two in particular struck a chord with me.

In his piece, Dr. Diponkar Banerjee noted that, when he became president, “the CAP was struggling with some of the unilateral decisions made by the Royal College of Physicians of Canada regarding the restructuring of laboratory medicine training programs.” The furor over the status of neuropathology and general pathology programs has abated, but it is far from certain that they will remain primary disciplines in the long term. What was disconcerting about the Royal College approach to these programs was the fact that pathologists and laboratory physicians appeared to have little say in the matter. Scant attention was paid to the societal need for general pathologists in many parts of this country or the fact that many of the international leaders of neuropathology trained in Canadian neuropathology programs. It seems likely that the future of these two programs will be revisited, perhaps repeatedly or until the Royal College succeeds in eliminating them. This past August there was an announcement that the Committee of Specialties of the Royal College had endorsed a proposal that medical biochemistry cease to be a primary discipline and become a subspecialty of internal medicine or pediatrics. The Office of Education was to conduct a consultation with stakeholders, but, as I write this in late October, it is far from clear that this will include the wider community of pathologists and laboratory physicians. In future issues of the journal, I hope to explore further the arguments about residency training in the laboratory disciplines.

While the Royal College concentrates on the implementation of educational principles, many pathologists feel that it has neglected its role in fostering the development of its professional disciplines. Given the number of training programs it accredits, this is perhaps inevitable. Nevertheless, it clearly puts Canadian pathologists and laboratory physicians at a disadvantage compared with our colleagues in the United Kingdom and Australasia. Some of the recent problems that have focused public attention on pathology would have been dealt with more effectively by the Royal College of Pathologists (U.K.), which has long had an established process for dealing fairly and expeditiously with pathologists whose performance has been judged to be substandard.

Dr. Paul Manley, in his reminiscence, speaks of the need for “one national pathology association to make a meaningful and thoughtful contribution to continuing education of laboratory professionals, and to residency teaching and preparation for … professional careers.” The CAP-ACP has an important role in this, but we cannot ignore the successful professional societies that the biochemists and microbiologists have established. Perhaps the time is ripe for the creation of a national umbrella organization, along the lines of an independent (Royal) College, that will protect the interests of all laboratory disciplines and bring us closer together, rather than pushing us farther apart. Although there have been examples of first-class diagnostic laboratories run by clinicians, with the administrative and scientific complexity of modern laboratory practice I have concerns that any reversion to this arrangement would not be in the best interests of the patients we serve or those we teach.

Whether you agree or disagree with my personal opinion, I invite you to share your thoughts with your colleagues in the correspondence pages of the journal. This subject, above all, is worthy of debate.

J. Godfrey Heathcote
Editor-in-Chief
Deux des articles d’anciens présidents de CAP-ACP relatant leurs souvenirs, parus dans le premier numéro de la revue, ont particulièrement capté mon attention.

D’abord, celui du Dr Diponkar Banerjee qui souligne que, lorsqu’il est devenu président de l’Association, « CAP-ACP était en désaccord au sujet de décisions unilatérales du Collège royal des médecins et chirurgiens du Canada à propos de la restructuration des programmes de formation en médecine de laboratoire. » Le tollé soulevé par la question des programmes de neuropathologie et de pathologie générale s’est apaisé, mais c’est loin d’être certain que ces deux disciplines conserveront leur position à long terme. Ce qui nous a déconcertés dans l’attitude du Collège royal est le fait que les pathologistes et les médecins de laboratoire n’ont pas eu voix au chapitre manifestement. Le Collège n’a pas accordé beaucoup d’importance aux besoins sociétaux en pathologistes généraux dans nombre de régions du pays ni au fait que de nombreux neuropathologistes chefs de file dans leur domaine sur la scène internationale ont été formés au Canada dans les programmes en vigueur. Selon toute probabilité, l’avenir de ces deux programmes sera débattu encore et encore ou jusqu’à ce que le Collège royal parvienne à les éliminer. Le Comité des spécialités du Collège royal a entériné en août dernier la proposition voulant que la biochimie médicale ne soit plus une discipline primaire, mais une surspécialité de la médecine interne ou de la pédiatrie. Le Bureau de l’éducation doit consulter des intervenants sur ce sujet, mais, au moment où j’écris ces lignes, soit la fin d’octobre, on ne sait toujours pas si la grande communauté des pathologistes et des médecins de laboratoire sera du nombre de ces intervenants. Dans de prochains numéros de la revue, j’espère pouvoir aborder en profondeur l’argumentation sur la formation en résidence dans les disciplines de laboratoire. Cependant que le Collège royal se concentre sur la mise en œuvre de principes éducatifs, les pathologistes sont nombreux à estimer qu’il néglige son rôle de promotion du perfectionnement de ses disciplines professionnelles. Étant donné le nombre de programmes de formation qu’il agré, cela est sans doute inévitable. Néanmoins, cette situation est nettement désavantageuse pour les pathologistes et les médecins de laboratoire canadiens par rapport aux collègues du Royaume-Uni et de l’Australasie. Il appert que le Collège royal des pathologistes du Royaume-Uni, qui a établi voilà longtemps déjà un processus juste et expéditif de rectification du rendement non conforme aux normes, aurait su régler efficacement et promptement certains des problèmes en pathologie qui ont suscité l’inquiétude du public récemment.

En se remémorant son passage à la présidence, le Dr Paul Manley aborde la nécessité « qu’une association canadienne de pathologie contribue véritablement à la formation continue des professionnels de laboratoire, ainsi qu’à l’enseignement durant la résidence et à la préparation en vue… de la carrière. » CAP-ACP a un rôle important à jouer sur ce plan, mais nous ne pouvons ignorer les sociétés professionnelles très actives qu’ont formées les biochimistes et les microbiologistes. Peut-être le moment est-il propice à la création d’une organisation de coordination pancanadienne, à l’image d’un collège (royal) indépendant, qui défendrait les intérêts de toutes les disciplines de laboratoire et nous rapprocherait, plutôt que nous éloigner, les uns des autres. Il y a eu bien sûr des laboratoires exemplaires à vocation diagnostique dirigés par des cliniciens, mais je suis convaincu qu’un retour en arrière de la sorte ne serait pas bénéfique pour nos patients ni pour nos étudiants au vu de la complexité administrative et scientifique de la pratique de laboratoire moderne.

Que vous soyez d’accord avec moi sur ce sujet ou pas, n’hésitez pas à me faire part, ainsi qu’à vos collègues, de vos observations dans le courrier des lecteurs. S’il est un sujet dont il faut débattre, c’est bien celui-là.

J. Godfrey Heathcote
Rédacteur en chef
Message from the President

Dear CAP-ACP Members,

I am delighted to be able to update you on a number of projects that the CAP-ACP Executive has been working on since our successful 60th Annual Meeting in Halifax in July. The many seeds that our previous president, Jagdish Butany, sowed have germinated, and the young seedlings are starting to flourish.

As you may have noticed, we are using the acronym CAP-ACP rather than CAP to refer to our organization. This not only avoids confusion with the College of American Pathologists (CAP) but, more importantly, symbolizes the national nature of our organization, inclusive of our colleagues in Quebec and New Brunswick.

Speaking of the CAP, we continue our collaboration with them on the development of synoptic reporting for cancer specimens and are close to finalizing a memorandum of understanding regarding the use of CAP checklists and Canadian representation on the CAP cancer checklist committees. The CAP-ACP is very grateful to the Canadian Partnership Against Cancer (CPAC), which is playing a major role in facilitating this collaboration, with the help of John Srigley and Andrea Maclean.

CPAC is also supporting our continuing professional development with a generous grant and is facilitating participation by patient interest groups in the CAP-ACP Council. The CAP-ACP has now finalized an agreement with objective pathology to assist with the development of online continuing professional development, under the leadership of Joan Sweet.

The CAP-ACP is working with Accreditation Canada and the Canadian Standards Association to evaluate and develop an action plan to improve and streamline laboratory accreditation in Canada with the input of existing provincial accreditation bodies. We are also participating in the Royal College Task Force on Laboratory Medicine and hope to increase communication with provincial pathology associations on matters of common interest. A number of subcommittees are working, including a Task Force on the Development of Guidelines for Investigation of Irregularities in Laboratory Medicine, chaired by Diponkar Banerjee, a Mission Statement Committee, chaired by Chris Naugler, and a committee developing guidelines for KRAS testing, chaired by Alan Spatz.

The document “Best Practice Recommendations for Standardization of Immunohistochemistry Tests,” developed under the leadership of Emina Torlakovic, has been accepted for publication in the American Journal of Clinical Pathology, and the document “Guidelines for Measurement of Pathologist Workload” is being prepared for publication by Raymond Maung.

The Annual Meetings Committee, with annual meetings chair Avrum Gotlieb, local organizing chair Dragana Piladvzic, continuing professional development chair Joan Sweet, and a number of section chairs and other members, is putting together an excellent program for the upcoming Annual Meeting in Montreal. There will be an emphasis on quality issues, and the meeting will feature the debut of new special interest groups in areas such as international health and informatics.

At the CAP-ACP Secretariat, all the above activity is calmly kept on track by our administrator, Daniele Saintonge. We welcome input from the membership on any matter of interest to the community of pathologists and encourage your active involvement.

Best wishes for a blessed Hanukkah, Christmas, and New Year.

Laurette Geldenhuyys
President
Obituaries

Dr. George Anderson (1928–2009)
Dr. George Anderson was born in 1928 in Edinburgh, Scotland, and received his medical degree from Guy’s Hospital in London. He immigrated to Canada in 1956, and after a year’s internship at the Royal Victoria Hospital in Montreal, took his pathology training at the Ottawa Civic Hospital and was certified by the Royal College of Physicians and Surgeons of Canada in 1961. He was staff pathologist at the Ottawa Civic Hospital from 1961 to 1968 and served as medical director of the Red Cross Blood Transfusion Service for Eastern Ontario from 1961 to 1965. From 1968 to 1974, Dr. Anderson was associate director of the Department of Pathology at the Royal Jubilee Hospital in Victoria, and from 1974 to 1979, was director of the Cytology Service at the Victoria General Hospital in Halifax. In 1979, Dr. Anderson moved to Vancouver to become director of laboratories at the Cancer Control Agency of British Columbia, and from 1985 to 1993 was the director of the Division of Cytology at the BC Cancer Agency. As member of the Canadian Society of Cytology since 1961, Dr. Anderson served as secretary-treasurer and president in the early days and as secretary on a second occasion from 1979 to 1982, and was president for the second time from 1990 to 1991. Dr. Anderson retired in Victoria in 1997, and he died in 2009 at the age of 81.

Dr. Michael McNeely (1944–2009)
Dr. Michael McNeely was born in Toronto in 1944 and received his early schooling in Victoria, British Columbia. He obtained his medical degree from the University of Manitoba in 1969, and then trained in laboratory medicine at Hartford, Connecticut, with Dr. William Sunderman until 1973. He received a fellowship in medical biochemistry in 1974. For a short while, he worked at Mount Sinai Hospital in Toronto, but in 1976, returned to Victoria where he was laboratory director and president of the Medical Laboratories until 2005. After his retirement from the laboratory, he worked as a consultant to the BC government for the Electronic Health Services Project. He was a pioneer in the field of medical informatics and made some of his most important contributions here. Dr. McNeely was nominated as an honorary member of the CAP-ACP in 2004 and received the Distinguished Service Award. Dr. McNeely passed away in the fall of 2009.
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Dr. Butany Honoured by CAP

Dr. Jared Schwartz (right), president of the College of American Pathologists (CAP), presents the Presidents Certificate and Silver medal, honouring Dr. Jagdish Butany (past president of the Canadian Association of Pathologists), October 9, 2009, in Washington, DC, at the CAP House of Delegates Annual Dinner.
The Pathologist as an Expert Witness

Harry E. Emson, MA, MD, FRCPC

In the past, pathologists in most parts of Canada could make a choice as to their involvement with the legal system, and its degree. Pathologists could choose whether or not to do medicolegal autopsies either in a coroner’s or medical examiner’s system. However, in the more remote and less populated regions, involvement with the legal system was not always possible to decline and circumstances could arise anywhere in which pathologists, from no desire or choice of their own, found themselves involved with cases that proceeded to court hearings and in which they were summoned to give evidence. For all of us, it is necessary to consider this eventuality in advance and to define our beliefs and attitudes in the event of becoming involved in the legal system.

The legal system in Canada, in those of its aspects with which a pathologist may become involved, is almost entirely based on the adversarial principle. Lawyers are trained in this way from their first day in law school. It permeates and imbibes their lives, and many of them find it difficult or impossible to think in any other way. This principle believes that a legal case is best solved by reducing it to a single simple question and deciding the answer by a court hearing before a judge, often sitting with a jury, and conducted as a gladiatorial contest in which the parties to the controversy are represented by lawyers – “advocates” acting as “counsel.”

The questions are put to witnesses in various ways, and the answer to each individual question is sought in opposing terms – yes or no, right or wrong, black or white. On the sum of these answers, the judge or jury decides the answer to the question posed: for example, did A kill B under the circumstances defined by the law as murder? Pathologists do not think in this way, nor do any physicians. They seek a much vaguer and ill-defined concept of the total truth of a situation, which in many cases remains fuzzy around its edges, despite all attempts at clarity and precision. They find the adversarial method alien, frequently frustrating, unproductive, and often unpleasant. However, when summoned to court, we are on the law’s grounds and, to a degree, are subject to its rules. Commitment to the adversarial system is implicit from the first formal contact, the subpoena to a witness, that identifies the witness as being summoned because he or she is thought able to give evidence for one side of the case or the other; it explicitly conscripts the pathologist onto one side, one team, usually that for the prosecution.

It is very easy to find fault with the adversarial system, and to pick holes in it, until one tries to find a better alternative; and in any event, this option is not in practice open to us. It does break down very obviously in some of its applications, and to some extent, the law has accepted this and sought alternatives, notably in family law, with which the pathologist is rarely concerned. In the courtroom, the adversarial system entitles counsel to the most minute inquiry into the credentials, training, experience, and beliefs of the witness, which is legitimate; although questions based on false implications of the type, “When did you stop beating your wife?” may also be raised.

The desire of the law for a single simple answer and the belief of the pathologist in complex and interacting multiple causes may be a source of frustration. I remember from my early years in Saskatchewan a case in which a young woman died. She had been beaten more spectacularly than seriously, was drunk, and was exposed to a cold winter night. I stated that these factors all contributed to her death and that I could not quantify the contribution of each. I got into deep trouble in the witness box for sticking to this opinion rather than isolating a single cause of death. I think it was fortunate that in those days I was a stubborn young man – some said pig-headed – and the case did encapsulate for me at an early age some of the problems I was going to face if I chose to continue in medicolegal work.

It may be difficult for the pathologist not to become a partisan, for instance, in the death of a child following sexual assault. The pathologist is never in possession of all the facts of a case; he or she has performed a minute and exact analysis of a small section of the evidence, which may be conclusive in such matters as a cause of death but totally lacking in other circumstances surrounding the death. If the facts are clear, their interpretation may be the subject of different opinions. For instance, regarding orbital hematomas in death from a gunshot wound of the head, are these the result of antecedent external assault or of increased

Harry E. Emson, MA, MD, FRCPC, is emeritus professor of pathology at the University of Saskatchewan and holds a diploma in medical law and ethics. He is based in Saskatoon, Saskatchewan.
intracranial pressure? Or how did an overdose of a toxic substance come to be taken? – a question better addressed within the expertise of a toxicologist. Whenever pathologists step outside their very narrow bounds of certainty, they should bear in mind, irrespective of their personal religious belief, the words of Oliver Cromwell: “I beseech thee, in the bowels of Christ, think it possible that ye may be mistaken.” There is one type of counsel, much more dangerous than the old exponents of bluff and bluster, who will profess incompetence in the subtleties of medical evidence, flatter the witness into an inflated belief of his or her own omniscience, and, having lured the pathologist onto the tip of a bough of speculation, briskly saw it off at its proximal end. One phrase that the pathologist should never be afraid of using is, “I do not know.”

There is another, antithetical belief in the role of the expert witness to which the law pays some attention. This is to regard the expert witness as an independent person bringing education, training, and experience to the court as a whole rather than to one side of the case or the other, in the hope that this may assist the court to come to a just conclusion. Although this is sometimes more of a token genuflection than a true commitment, the Goudge Inquiry in Ontario did emphasize its importance. The expert is neither a partisan nor an advocate, hired by one side or the other; though under the adversarial system, counsel for either side will endeavour to extract from the expert’s evidence those facts and opinions that favour their side of the case. The pathologist is independent, impartial, and objective, a witness for the court, not for either of the parties to the case. This is an austere, and some might say self-righteous, belief, but I think it is the correct one.

This is the ethos and attitude in which I believe. I have tried to practise and teach this principle all my professional life and to swim against the strong current that endeavours to involve me as an adversary. This is not easy when the Crown and defence counsel are clearly adversaries. Other pathologists have adopted the opposite view and consciously accepted their recruitment to a “team,” most commonly that of the Crown and the prosecution. The perception of the independent and impartial expert may be diminished when the first contact with the legal system, that is, the receipt of a subpoena, is to appear as a witness for either the defence or Crown. In the official view, the witness is believed capable of giving evidence to support one side of the case or the other. For the pathologist, this most commonly means for the prosecution, and any notion of impartial objectivity can be firmly squashed at the outset.

It would make things far easier for the pathologist if he or she were summoned by the court, rather than by one side of the case or the other. I understand that this possibility is open, but I have never known it used. Its use would not, and should not, prevent the subpoena of other expert witnesses by the opposing sides to the case, particularly where evidence is of opinion and interpretation rather than of fact; but it would endorse the ideas of independence, non-partisanship, and objectivity that I believe to be integral to the expert. However, in practical terms, and from my experience, I think this is most unlikely to happen. The adversarial attitude is too deeply ingrained in the law and the thinking of lawyers. The best that we can hope for is that pathologists educated in the requirements of the criminal justice system will practise in the manner and in the beliefs that I have suggested are correct and manage to resist the forces propelling them into the adversarial attitude, as well as the temptations of its adoption.

There is one risk that the pathologist as witness will continue to run under any system, and that is of perceiving himself or herself as the righter of wrongs, the crusader for the downtrodden, the knight on the white charger standing for truth and justice against evil and oppression. This is a heady intoxicant and as dangerous as all intoxicants taken at the wrong time in the wrong place. It may well lead in short order to domination of opinion over fact, wilful distortion of evidence, and the attempted imposition of one’s own judgment over that of the court. I would be the last person to suggest that courts, judges, and juries are infallible, but they are less fallible than individual judgment fortified by a stiff dose of self-delusion. The pathologist as witness needs a mastery of the facts, an admission of where the facts are partly known or unknown, an absolute differentiation between fact and opinion, and an ultimate capacity to admit his or her own limitations – “I do not know.” In almost 50 years in the part-time practice of forensic pathology, I can count on my fingers the cases into which I have gone feeling that I had a duty to try to prevent a miscarriage of justice or to rectify injustice where it had been caused by poor pathology. What I think we should do, I have tried to spell out above, as a pragmatic creed forged on the anvil of hard experience.
**Lymphomas of the Breast: A Clinicopathological Study Over 12 Years**

Monalisa Sur, MBBS, FCPath (SA), FRCPath (UK), FRCPC, Prashant K. Dhamanaskar, MBBS, MD, FRCPC, Noori Akhtar-Danesh, MSc, PhD (Newcastle), Leela Elavathil, MD, FRCPC

**ABSTRACT**
Non-Hodgkin’s lymphomas of the breast are rare and represent 0.04–0.50% of malignant lesions of the breast. Most cases are of a B-cell phenotype and are more commonly identified on the right side. This series summarizes our experience at a regional cancer centre over the past 12 years with all cases of lymphoma of the breast based on the World Health Organization (WHO) 2008 classification. We analyzed the clinicopathological and immunophenotypical characteristics of 40 breast lymphomas and the relative frequency of primary versus secondary lymphomas. Statistical analysis of survival data based on disease progression, frequency of primary versus secondary origin, and subtype in the WHO classification were also assessed.

In our series of 40 breast lymphomas, primary lymphoma was more common (63%) than secondary lymphoma (37%). Involvement of the right breast (63%) was significantly more frequent than that of the left breast (35%). Only one case of T-acute lymphoblastic lymphoma (T-ALL) showed bilateral breast involvement. Overall, B-cell lymphomas constituted the majority of lymphomas (88%). Diffuse large B-cell lymphoma (DLBCL) was the most common subtype (40%), followed by MALT lymphoma and follicular lymphoma (20% each). B-chronic lymphocytic lymphoma/leukemia constituted only 5% of the lesions. DLBCL was the most common subtype of both primary and secondary lymphomas. Rarer subtypes (20%) included nasal natural killer/T-cell lymphoma, T-ALL, B-acute lymphoblastic lymphoma, peripheral T-cell lymphoma, and anaplastic large-cell lymphoma. The overall 5-year and 10-year survival rates were 78% and 67%, respectively. In our series, patients with secondary lymphoma involving the breast and those with high-grade histology fared worse than those with primary involvement and low-grade histology. Thus, the histological subtype, type of involvement (primary versus secondary), and stage of the disease affected the survival of these patients. All these factors should be taken into consideration in the management of breast lymphomas.

**RÉSUMÉ**
Les lymphomes non hodgkiniens du sein sont rares et représentent de 0,04 à 0,5 % des lésions malignes du sein. La plupart des cas présentent un phénotype de lymphocytes B et sont dépistés le plus souvent du côté droit. Cette série résume notre expérience des douze dernières années dans un centre régional de cancérologie, où tous les cas de lymphomes du sein ont été identifiés d’après la classification de 2008 de l’Organisation mondiale de la Santé (OMS). Nous avons analysé les caractéristiques clinico-pathologiques et immunophénotypiques de 40 lymphomes du sein et la fréquence relative des lymphomes primitifs par rapport aux lymphomes secondaires. Nous avons aussi effectué des analyses statistiques des données de survie, et ce, en fonction de la progression de la maladie, de la fréquence de l’origine primitive et de l’origine secondaire, et du sous-type (d’après la classification de l’OMS).
Dans la série de 40 lymphomes du sein, le lymphome primitif était plus fréquent (63 %) que le lymphome secondaire (37 %). L’atteinte du sein droit (63 %) était beaucoup plus fréquente que celle du sein gauche (35 %). Seulement un cas de lymphome lymphoblastique aigu à cellules T (LLA-T) présentait une atteinte bilatérale des seins. Dans l’ensemble, les lymphomes à cellules B constituaient la majorité des lymphomes (88 %). Le lymphome diffus à grandes cellules B (LDGCB) était le sous-type le plus fréquent (40 %), suivi du lymphome de type MALT et du lymphome nodulaire (20 % chacun). Le lymphome ou la leucémie lymphocytique chronique à cellules B constituait seulement 5 % des lésions. Le LDGCB était le sous-type le plus fréquent des lymphomes primitifs et secondaires. Le lymphome T/NK nasal, le LLA-T, la leucémie aiguë lymphoblastique à cellules B, le lymphome T périphérique et le lymphome anaplasique à grandes cellules représentaient des sous-types plus rares (20 %). Les taux de survie cinq ans et dix ans après le diagnostic étaient respectivement de 78 % et de 67 %. Dans notre série, les patientes atteintes d’un lymphome secondaire du sein et celles dont l’examen histologique montrait un degré élevé de malignité s’en sont moins bien sorties que celles atteintes d’un lymphome primitif ou dont l’examen histologique montrait un faible degré de malignité. Ainsi, on constate que le sous-type histologique, le type d’atteinte (primitif ou secondaire) et le stade de la maladie ont une incidence sur la survie de ces patientes. Tous ces facteurs doivent être pris en considération dans la prise en charge des lymphomes du sein.

Non-Hodgkin’s lymphomas (NHLs) of the breast are rare and represent 0.04–0.50 % of malignant lesions of the breast; they account for 1.7 to 2.2 % of extranodal NHLs and 0.38 % of all NHLs.1–5 Most cases are of the B-cell phenotype, and they more commonly occur in the right breast.6 Primary lymphomas have been defined by the criteria of Wiseman and Liao.7 This series summarizes our experience of lymphoma of the breast based on the World Health Organization (WHO) classification at our regional cancer centre over the past 12 years.8 We analyzed the clinicopathological and immunophenotypic characteristics of the breast lymphomas and the relative frequency of primary versus secondary lymphomas. Survival data were obtained for 37 cases from health records from the Juravinski Cancer Centre. Primary breast lymphomas were defined according to the criteria of Wiseman and Liao7:

1. Technically adequate pathological specimens
2. Mammary tissue and lymphomatous infiltrate in close association
3. No evidence of concurrent widespread disease other than ipsilateral axillary nodes occurring concomitantly with the primary breast lesion
4. No prior diagnosis of extramammary lymphoma

Cases that did not fulfill the above criteria and had a prior diagnosis of extramammary lymphoma were reclassified as secondary lymphomas. A breast pathologist and a hematopathologist independently reviewed the original slides according to the WHO 2008 Classification of Tumours of Haematopoietic and Lymphoid Tissue, and a consensus diagnosis was taken in cases of discrepancy. An immunohistochemistry panel (Table 1) was performed where relevant on formalin-fixed, paraffin-embedded tissue sections using the standard labelled streptavidin biotin (LSAB) technique.
Table 1. Antibody Panel Used for Diagnosis and Classification

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<thead>
<tr>
<th>Antibody</th>
<th>Manufacturer</th>
<th>Dilution</th>
<th>Antigen Retrieval</th>
<th>Clone</th>
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<tr>
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<td>Novocastra</td>
<td>1/500</td>
<td>Citrate, HIER</td>
<td>5A4</td>
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<td>CD3</td>
<td>Cell Marque</td>
<td>1/500</td>
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<td>Rabbit</td>
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<td>Citrate, HIER</td>
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<td>C8/37</td>
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<td>Citrate, HIER</td>
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</tr>
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<td>Citrate, HIER</td>
<td>56C6</td>
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<td>None</td>
<td>LeuM1</td>
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<td>Dako lo, HIER</td>
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<td>CD21</td>
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<td>Proteinase K</td>
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</tr>
<tr>
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<td>1B6</td>
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</tr>
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<td>Citrate, HIER</td>
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<td>Citrate, HIER</td>
<td>124</td>
</tr>
<tr>
<td>BCL6</td>
<td>Dakocytomation</td>
<td>1/50</td>
<td>Dako Hi, HIER</td>
<td>PG-B6p</td>
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<tr>
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<td>LabVision</td>
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<td>Dako lo, HIER</td>
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</tr>
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<td>1/1,000</td>
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<td>Dakocytomation</td>
<td>1/1,000</td>
<td>None</td>
<td>Rabbit</td>
</tr>
<tr>
<td>TDT</td>
<td>Novocastra</td>
<td>1/25</td>
<td>Dako lo, HIER</td>
<td>SEN28</td>
</tr>
</tbody>
</table>

HIER = heat-induced epitope retrieval.

For statistical analysis, cases were divided into low-grade lesions (follicular lymphoma [FL], B-chronic lymphocytic lymphoma/leukemia [B-CLL], and MALT lymphoma) and high-grade lesions (diffuse large B-cell lymphoma [DLBCL], acute lymphoblastic lymphoma [ALL], peripheral T-cell lymphoma [PTCL], natural killer/T-cell lymphoma [NK-T lymphoma], and anaplastic large-cell lymphoma [ALCL]). Statistical analysis was conducted using the Kaplan-Meier curve followed by log-rank test for overall survival, primary versus secondary cases, and high-grade versus low-grade lesions. Cox regression analysis was conducted to compare survival time between primary and secondary lymphomas and between low- and high-grade lesions. Because of the small sample size, we depicted Kaplan-Meier curves for only primary versus secondary cases, and high-grade versus low-grade lymphomas. Also, to increase the power of the test, Cox regression analysis was conducted to compare hazard ratio (HR) between primary and secondary lymphomas and between low- and high-grade lesions.

Results
All cases were reviewed and reclassified according to the WHO 2008 classification; only four cases needed revision of diagnostic nomenclature. One case of DLBCL was reclassified as primary MALT lymphoma of the breast. Two other cases were reclassified as MALT lymphoma from the initial diagnoses of B-chronic lymphocytic lymphoma/leukemia (B-CLL/small lymphocytic lymphoma [SLL]) and lymphoplasmacytic lymphoma. One case of MALT lymphoma was reclassified as atypical B-CLL/SLL. The major clinical and histopathological features of the
cases are summarized in Tables 2 and 3. DLBCL (Figure 1) was the most commonly encountered subtype (40%), followed by FL and MALT lymphoma (Figure 2), each constituting 20% of the breast lymphomas. The rarer subtypes accounted for the remaining 20% of the lymphomas (Table 4; Figure 3). Most cases of DLBCL demonstrated centroblastic morphology, with two cases showing immunoblastic and one case showing anaplastic morphology. Ten cases of DLBCL were of germinal centre B cell like (GCB) phenotype, and six cases showed non-GCB phenotype by immunohistochemistry. Two cases of each were secondary to the breast. The proliferation index, based on Ki67 expression, ranged from 40 to 75%.

**Table 2. Clinical Characteristics of Breast Lymphoma**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>40</td>
</tr>
<tr>
<td>Type of involvement</td>
<td>Primary: 25 (63%) &lt;br&gt; Secondary: 15 (37%)</td>
</tr>
<tr>
<td>Sex</td>
<td>All females</td>
</tr>
<tr>
<td>Laterality</td>
<td>Left: 14 (35%) &lt;br&gt; Right: 25 (63%)</td>
</tr>
<tr>
<td></td>
<td>Bilateral: 1</td>
</tr>
<tr>
<td>Age</td>
<td>Range: 34–86 y &lt;br&gt; Mean: 60 y</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Palpable mass (38/40 cases) &lt;br&gt; Screening mammogram/sonogram (2/40 cases); both primary, 1 MALT lymphoma, 1 B-CLL/SLL</td>
</tr>
<tr>
<td>Association</td>
<td>2/40 cases presented with mass during pregnancy – both primary DLBCL &lt;br&gt; 1 patient with FL had concurrent plasma cell myeloma &lt;br&gt; 1 patient with FL had concurrent infiltrating duct carcinoma</td>
</tr>
<tr>
<td>Phenotype</td>
<td>B-cell phenotype: 35 (88%) &lt;br&gt; T-cell phenotype: 4 (10%) &lt;br&gt; Natural killer/T-cell phenotype: 1 (2%)</td>
</tr>
<tr>
<td>Bone marrow staging</td>
<td>Positive: 7 (18%) (2/25 primary, 5/15 secondary) &lt;br&gt; Negative: 33 (82%)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>Range: 4 mo–10 y</td>
</tr>
<tr>
<td>Follow-up status</td>
<td>Dead from disease progression: 10 (25%) &lt;br&gt; Dead from unrelated disease: 9 (23%) &lt;br&gt; Alive with complete remission: 18 (45%) &lt;br&gt; Alive with disease: 3 (7%)</td>
</tr>
</tbody>
</table>

B-CLL = B-chronic lymphocytic lymphoma; FL = follicular lymphoma; SLL = small lymphocytic lymphoma.
LYMPHOMAS OF THE BREAST: A CLINICOPATHOLOGICAL STUDY OVER 12 YEARS

Table 3. Histopathological Types of Lymphoma

<table>
<thead>
<tr>
<th>Histopathological Type</th>
<th>Total (%)</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>16 (40)</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>8 (20)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>8 (20)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>B-chronic lymphocytic lymphoma/leukemia</td>
<td>2 (5)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>T-acute lymphoblastic lymphoma</td>
<td>2 (5)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>B-acute lymphoblastic lymphoma</td>
<td>1 (2.5)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>1 (2.5)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nasal type natural killer/T-cell lymphoma</td>
<td>1 (2.5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>1 (2.5)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>40</strong></td>
<td><strong>25</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

Figure 1. Diffuse large B-cell lymphoma of the breast. (Hematoxylin and eosin, original magnification 200x)

Figure 2. MALT lymphoma of the breast. (Hematoxylin and eosin, original magnification 200x)

Table 4. Rare Lymphoma Types Involving Breast

<table>
<thead>
<tr>
<th>Histopathological Type</th>
<th>Age (y)</th>
<th>Primary or Secondary</th>
<th>Recurrence</th>
<th>Follow-Up Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal type natural killer/T-cell lymphoma</td>
<td>51</td>
<td>Secondary</td>
<td>Progression</td>
<td>DOD – 12 mo</td>
</tr>
<tr>
<td>T-acute lymphoblastic lymphoma</td>
<td>54</td>
<td>Secondary</td>
<td>Axillary LN, local breast</td>
<td>DOD – 15 mo</td>
</tr>
<tr>
<td>T-acute lymphoblastic lymphoma</td>
<td>40</td>
<td>Secondary</td>
<td>Nil</td>
<td>CR – 3 y</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>41</td>
<td>Primary</td>
<td>Nil</td>
<td>CR – 7 y</td>
</tr>
<tr>
<td>B-acute lymphoblastic lymphoma</td>
<td>69</td>
<td>Primary</td>
<td>Nil</td>
<td>CR – 4 mo</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>71</td>
<td>Primary</td>
<td>Nil</td>
<td>CR – 5 y</td>
</tr>
</tbody>
</table>

CR = alive with complete remission; DOD = dead from disease; LN = lymph node.
For the secondary lymphomas, lymph nodes were the main sites of initial involvement, with extranodal sites such as the stomach, spleen, ovary, mediastinum, and nasal cavity in a few cases. At the time of diagnosis of breast lymphoma, seven patients (18%) had bone marrow involvement (stage IV disease). Two of these patients had primary low-grade breast lymphoma: MALT lymphoma and B-CLL/SLL. The remaining five cases with bone marrow involvement had secondary breast involvement by DLBCL (1), MALT lymphoma (1), and FL (3). The initial diagnosis of primary DLBCL was made at mastectomy in three patients. One patient with secondary DLBCL was treated with mastectomy and local radiotherapy (RT). Most patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a CHOP-like chemotherapy, with additional local RT in six patients. Local RT alone was given in nine patients who had low-grade lymphoma localized to the breast.

A total of 19 patients died during the follow-up period, 10 from disease progression and nine from unrelated diseases. The 10 patients who died from disease progression had survival periods ranging from 5 months to 7 years (median 19.5 months, mean 30.8 months). Eight of these patients had high-grade lymphoma: DLBCL in six, nasal NK-T lymphoma in one, and T-acute lymphoblastic lymphoma/leukemia (T-ALL) in one. Two patients had a low-grade lymphoma (FL and MALT lymphoma). The survival in these patients with high-grade lymphoma ranged from 5 months to 3 years (median 13.5 months, mean 19 months), and those with low-grade lymphoma survived for 6 and 7 years, respectively. Thus, histopathological type had a marked impact on the duration of survival. In the patients who died from their disease, three received chemotherapy and RT, three underwent mastectomy with one getting receiving RT, and four received chemotherapy alone. Of this group, seven patients had secondary breast involvement and two had primary involvement. This group showed recurrence in nodal and extranodal sites with large cell transformation in one and disease progression at the same site in two patients.

Nine patients died from unrelated disease, and all were in complete remission. Only two of these had regional lymph node recurrence, but they were treated successfully. The patients were
Disease free from 1 to 10 years (median 60 months, mean 55.6 months). Eighteen patients showed complete remission and were still alive at the last follow-up. Thirteen patients had primary while five patients had secondary breast involvement. DLBCL was the most common subtype followed by FL and MALT lymphoma. The other subtypes in this group included one case each of PTCL, ALCL, T-ALL, and B-ALL. Eight patients received local RT, seven received chemotherapy, and three received chemotherapy alone. The follow-up period ranged from 4 months to 9 years in this group (median 72 months, mean 62.4 months). Three patients were alive with disease after a follow-up of 4 months, 6 years, and 9 years, respectively (mean 16 months). All three lymphomas were low grade.

In our case series, the 5-year survival was 78% and 10-year survival was 67% by Kaplan Meier curves. Mean survival time was 7.90 years (SD = 0.60 and CI 95% 6.71–9.08). Based on the univariate analysis, there was marginally significant difference in the survival time between primary and secondarily lymphomas (Log rank test = 3.52, \( p = .061 \)) (Figure 4). There were significant differences in survival in patients with high-grade versus low-grade lymphomas (Log rank test = 3.72, \( p = .05 \)) (Figure 5). Survival analysis conducted using the Cox regression technique (multivariate) indicated that both the grade of the lesion and the type of involvement (primary versus secondary) had significant effects on the HR of death. \( p \) values for the effect of grade and primary versus secondary were .033 and .029, respectively, and HRs were 5.8 (CI 95% = 1.15–29.08) and 4.8 (CI 95% = 1.17–19.61), respectively. This implies that the risk of death from the disease in patients with a high-grade lesion is about 5.8 times greater than that of patients with a low-grade lesion. Similarly, the risk of death from secondary lymphoma is about 4.8 times that of primary lymphoma.
Discussion
Breast lymphomas are rare (0.04–0.05%) and account for 1.7–2.2% of extranodal lymphomas and 0.38% of all NHLs. In our study, all patients were females, with an age range of 34–86 years (mean 60 years). This finding is similar to previously reported series in which the peak age incidence was usually the sixth decade. Based on the criteria of Wiseman and Liao, 25 were primary (63%) and 15 were secondary (37%) lymphomas of the breast. Other studies have reported slightly more secondary lymphomas than primary lymphomas of the breast. The right breast was involved in 25 patients and left breast in 14 patients; one case showed bilateral involvement by a secondary T-ALL. This tendency to right breast preponderance has been reported previously and remains unexplained. In 15% of cases, breast lymphomas may occur during pregnancy or lactation. In this series, two cases presented with a breast mass during pregnancy. Both patients were diagnosed with primary DLBCL and were treated with chemotherapy and local radiation after successful completion of pregnancy. Both patients are alive and in complete remission with a follow-up period of 4 and 9 years, respectively. The majority of our patients (38/40) presented with a palpable mass. In two patients, the lymphoma was detected by mammogram/sonogram during breast screening and was diagnosed histopathologically as primary MALT lymphoma and B-CLL/SLL, respectively. There are no specific radiological features that would suggest a diagnosis of lymphoma over breast carcinoma, and mammographic findings vary from a discrete mass with marginal spiculation to a diffuse increase in parenchymal density. Most primary breast lymphomas are of B-cell phenotype. Primary T-cell lymphoma of the breast is uncommon, accounting for 3% of all cases. In our series, 88% were of B-cell phenotype, 10% were of T-cell phenotype, and 2% of NK-T-cell phenotype. Overall, DLBCL was the most common subtype (40%), followed by FL and MALT lymphoma (20% each) and B-CLL/SLL (5%). Many series have reported a predominance of DLBCL, with the incidence of follicular lymphoma ranging from 0 to 66%. There is one case series in which primary MALT lymphoma of the breast was the most common subtype, comprising 64.3%, and MALT lymphoma has been reported in other series with a frequency ranging from 0 to 44%. Although a definitive cause for the increased incidence of MALT lymphoma in some case series is not apparent, geography may have an unexplained role. Twenty percent of our cases were rare subtypes that included T-ALL with bilateral breast involvement, NK-T lymphoma, B-ALL, ALC, and PTCL (see Table 3). The first two patients with secondary involvement of the breast from other extranodal sites died of disease within 15 and 12 months. The latter three patients had primary involvement of the breast and remain in complete remission after treatment. The series of T-cell lymphomas of the breast reported by Aguilera et al. (two PTCLs, one ALC, and one NK-T lymphoma) suggested that these tumours have an aggressive clinical course. Another interesting feature of our series was the absence of central nervous system (CNS) dissemination; in other series, CNS involvement ranged from 2 to 27%. While the reason for this difference is unclear, it is possible that cases in our series were diagnosed earlier and treated more aggressively. Clinicians should be aware of the possibility of CNS spread in patients with breast lymphoma, and diagnostic imaging of the brain should be performed if patients develop neurological symptoms. CNS prophylactic treatment is controversial, and it is recommended that patients be followed up closely for signs and symptoms of CNS relapse and not be given prophylaxis routinely. In our study, most of the primary lymphomas were stage I, with only two cases showing bone marrow involvement at the time of initial diagnosis. All secondary lymphomas were stage III or IV. Most patients received chemotherapy with or without local RT, with four undergoing mastectomy. The 5-year survival was 78%, and 10-year survival was 67% by Kaplan-Meier curves. Mean survival time was 7.90 years (SD = 0.60 and CI 95% = 6.71–9.08). These results show a distinct improvement in survival time when compared with the initial report of Wiseman and Liao in 1972, which suggested a poor prognosis for patients with breast lymphoma treated with surgery with or without RT. In that series, the longer survivors received a radical mastectomy and RT. In a series from the Mayo Clinic by Wong et al., the 5-year survival rate was 70%, and the relapse-free survival rate survival rate was 42%. In other published series, the 5-year survival rates for patients with stage I
disease ranged from 61 to 89% compared with 0 to 50% for stage II disease.\textsuperscript{1,15,18,27–31} In the series by Vigliotti et al., the 10-year survival rate was 71% and compared favourably with most reported series including patients treated with chemotherapy, RT, or both.\textsuperscript{32} In a review of 380 cases reported from 1950 to 2002 in Japan, the findings regarding age, laterality, and histological subtype were similar to those in other reported series.\textsuperscript{33} The 5-year survival rate of breast NHL was 37.6% among all cases, urvival declining with advancing stage of disease. The authors also stated that minimum surgery for histological diagnosis was necessary for therapeutic planning and to determine prognosis in the treatment of the primary breast NHL. A more recent large study by Talwalkar et al. classified breast lymphomas using the WHO 2008 classification and divided the lymphomas into localized and disseminated groups.\textsuperscript{34} DLBCL was the most common in the localized group, with FL being the most common in the disseminated group. In their series, there was a significant difference in the disease-free survival between localized and disseminated DLBCL (\(p = 0.003\)). DLBCL in the disseminated group had a worse disease-free survival compared with that of FL or MALT lymphoma in the same group.\textsuperscript{34} In our series, patients with secondary breast lymphoma and high-grade histology fared worse than those with primary involvement and low-grade histology.

In the diagnosis and management of breast lymphomas, strict criteria should be used to determine whether the lymphoma is primary or secondary since this impacts overall survival. Breast lymphomas should be graded and subclassified based on the WHO 2008 classification, and hematopathological consultation should be obtained. Our study confirms that histological subtype, type of involvement (primary versus secondary), and stage of disease affect the survival rate and should be taken into consideration.

References

Tissue Engineering the Nucleus Pulposus: Is It Feasible?

Emma V. Dare, PhD, Rita A. Kandel, MD

ABSTRACT
Regenerative medicine aims to restore diseased or damaged tissues of the body and, as such, is the ultimate form of personalized medicine. Cells, scaffolds, and tissue integration together with vascularization are fundamental to the success of this approach. This review provides a synopsis of the current strategies and challenges for regenerative medicine using the nucleus pulposus, a tissue present in the intervertebral disc, as an example. The pathologist may one day be required to provide tissues or cells to facilitate this treatment approach.

RÉSUMÉ
La médecine régénératrice a pour but de remplacer les tissus malades ou endommagés; en ce sens, elle représente la forme ultime de la médecine personnalisée. Cellules, supports, implantation tissulaire et vascularisation en sont les éléments fondamentaux. L’article de fond offre un aperçu des stratégies et des défis actuels dans l’utilisation du noyau gélatineux, présent dans le disque intervertébral, en médecine régénératrice, à titre d’exemple. Le pathologiste sera peut-être un jour celui qui fournira les tissus ou les cellules nécessaires à la médecine régénératrice.

Regenerative medicine is an emerging field that combines many disciplines, including cell and molecular biology, engineering, polymer science, and clinical medicine, with the goal of regenerating diseased or damaged tissues and organs in the body. The aim is not only to replace the tissue that is malfunctioning but to provide a replacement that stimulates and supplies elements necessary for the body’s natural repair mechanisms. It has been estimated by the U.S. National Academy of Science that more than a hundred million patients in the United States with conditions such as cardiovascular disease, autoimmune diseases, diabetes, cancer, neurodegenerative diseases, arthritis, and burns could benefit from regenerative medicine strategies. Importantly, this approach will obviate the need for surgery or the use of drugs, with all their potential side effects.

To regenerate a tissue, a number of different approaches may be taken. Acellular scaffolds, which rely on and direct cell ingrowth from the surrounding tissues, can be implanted. Alternatively, cells alone or combined with a carrier such as a scaffold or hydrogel can be used. When cells are used for tissue regeneration, a cell source must be identified. Cells may be obtained from either a biopsy of donor tissue or a bone marrow aspirate, although other options are currently being developed. The cells must be expanded and then either differentiated in culture and injected back into the host or seeded onto a scaffold and implanted before or after in vitro culture (Figure 1). Culture in vitro allows for tissue formation prior to implantation, a feature that may be critical for rapid integration and function after implantation. The cells can be from a source that is heterologous (different species), allogeneic (same species but different individual), or autologous (same individual). The use of xenogeneic or allogeneic cells is controversial. Autologous cells are ideal as they do not incite an immune response and thus avoid the complications associated with...
immune-modulating drugs. Identifying a cell source for an organ that has multiple components – such as the heart, which has myocardiocytes, endothelium, pacemaker cells, coronary arteries, and valves – is daunting. Integration and vascularization add other levels of complexity. Clearly regenerative medicine as a therapy is still in the early stages of development. At present, it seems that tissues composed of a single or at most two cell types – such as nucleus pulposus (NP) or articular cartilage – and are avascular are more likely to be the first tissues treated using this approach. This review summarizes the current research into the regeneration of the NP, a tissue present in the intervertebral disc (IVD).

The extracellular matrix of the NP consists mostly of collagen type II\textsuperscript{10} and proteoglycans such as aggrecan\textsuperscript{11} and versican.\textsuperscript{12} The cells of the NP are primarily small chondrocyte-like cells with a possible second population of notochordal cells, depending on the age and species.\textsuperscript{13} Notochordal cells can be distinguished from the NP cells morphologically because they are larger and contain vacuoles and are surrounded by myxoid matrix (Figure 3).\textsuperscript{13,14} The exact role that notochordal cells play in the formation of the NP has not been fully elucidated. Histologically, IVD degeneration is marked by disc thinning and a merging of the annulus fibrosus and NP tissues. Cell viability and proteoglycan and tissue water content all decrease with an increasing degree of tissue degeneration in the NP.\textsuperscript{15} Alterations in the NP cause the annulus fibrosus

The cartilage end plates mark the transition between the IVD and the vertebra (Figure 2).\textsuperscript{8} The relationship between the tight lattice of the annulus fibrosus and the semifluid NP is important in providing the biochemical properties of IVD necessary for spinal stability.\textsuperscript{9}

Figure 2. Histological section of a human intervertebral disc from a female fetus at 20 weeks’ gestation. Notochordal cells (NC) are located at the centre of the nucleus pulposus. Note that the annulus fibrosus is not visible in this photograph. CEP = cartilage end plate. (Hematoxylin and eosin; bar = 100 µm)
to support more load, and the added stress can lead to tears, bulging, rupture, and herniation of the disc.\textsuperscript{16} It is likely that the avascular nature of the IVD compromises its ability to repair the damage.\textsuperscript{17,18} Treatment options include the surgical removal of disc material to alleviate nerve impingement, fusion and internal fixation to stabilize adjacent vertebrae, or disc replacement with a prosthesis.\textsuperscript{19,20} These treatments are not always successful and have the potential for serious complications.\textsuperscript{21} It is evident that there is a need for a more effective treatment for disc degeneration, and a biological approach would be optimal as it would preserve joint motion and allow for remodelling in response to loading.

Figure 3. Monolayer culture of bovine nucleus pulposus cells. Vacuolated notochordal cells are indicated by white arrows. (Bar = 50 µm)

Tissue Engineering of the IVD
As the extracellular matrix of the NP is so important to its function and physiological properties, regenerating an NP that has the appropriate composition is critical. To accomplish this, two issues must be addressed – the scaffold/environment and the cells.

Scaffold Materials
Biomaterials utilized in tissue engineering are important as they are able to stimulate specific cellular responses at the molecular level\textsuperscript{22} and can regulate cell and matrix orientation. Biomaterials need to have certain characteristics to be useful for tissue engineering.\textsuperscript{23,24} The biomaterial must be biocompatible and biodegrade into nontoxic products at the same rate as the tissue being regenerated. Scaffolds are one type of biomaterial and are three-dimensional porous structures. The scaffold should have a porous network to allow for tissue ingrowth or formation and nutrient delivery. The mechanical properties of the scaffold should be sufficient to support functionality, which for orthopedic applications would be weight bearing together with mechanical stability and mobility.\textsuperscript{9} Natural polymers (e.g., collagen, fibrin, alginites, chondroitin sulphates, and chitosan) and synthetic polymers (e.g., polyglycolide, polylactide, and polyhydroxybutyrate) are just some of the biomaterials that have been used for the regeneration of musculoskeletal tissues.\textsuperscript{25} Synthetic polymers are of great interest because they enable better control over the physical and chemical properties of the scaffolds.\textsuperscript{26} For example, poly(vinyl alcohol) hydrogels have been implanted as acellular NP replacements into the lumbar IVD of baboons.\textsuperscript{6} The implants were well tolerated over 24 months in vivo; however, the extrusion (herniation) rate remained high (20%). Natural materials have structures that more often resemble the native tissue environment. Halloran et al.\textsuperscript{27} created a scaffold composed of the macromolecules of the native NP extracellular matrix, which appears to favour NP tissue formation. The scaffold was composed of enzymatically cross-linked atelocollagen (a water-soluble form of collagen) type II with varying concentrations of aggrecan and hyaluronan molecules present in the extracellular matrix of the NP. Other materials can also be used as substrates to support NP tissue regeneration. Calcium polyphosphate, which is a bone substitute, has been used for this purpose. NP tissue can be formed on and integrated with the underlying substrate after seeding cells on its top surface.\textsuperscript{28} The substrate, when placed into the bone, is fixed in place by bony ingrowth. It is also possible to induce repair by in situ injection of a material in the absence of cells. Wang et al.\textsuperscript{29} implanted non-cell-based materials into porcine discs in order to stimulate tissue growth and increase the disc functional integrity. It was found that discs with implanted gel-foam (absorbable gelatin sponge) had the best integrity after 2 months. Injection of platelet-rich plasma (containing growth factors)
TISSUE ENGINEERING THE NUCLEUS PULPOSUS: IS IT FEASIBLE?

Encapsulated in gelatin microspheres, as an in situ biomaterial scaffold, into the NP of degenerate rabbit IVDs slowed down the disease process as a result of the added tissue structure, compared with results in animals that did not receive the treatment. Although there has been great progress in NP tissue engineering, few in vivo implantation studies have been performed to date. The optimal biomaterial that will induce or support in situ regeneration of NP tissue has yet to be identified.

Cell Source
As well as the optimal scaffold for NP tissue engineering, another important component of the system is the cells. One of the major issues limiting the clinical application of regenerative medicine is the identification of a cell source, which has to be easily harvested and allow cell number expansion before reimplantation. There are an estimated 4,000 cells/mm³ in the normal human NP. Expanding the number of NP cells in culture to obtain sufficient numbers for regeneration may result in de-differentiation of these cells. It has also been shown that IVD cells can exhibit cellular senescence, which may lead to altered phenotype and proliferation. Although it is possible to isolate normal cells from a non-degenerate disc, they may not be suitable for use. For example, it has been shown that a polymorphism (Trp2 allele) in the COL9A2 gene encoding the alpha-2 chain of collagen IX can predispose an individual to disc degeneration. Non-degenerate discs from these individuals were found to be mechanically inferior to non-degenerate normal discs from individuals without the polymorphism, suggesting that the use of genetically altered primary cells isolated from an otherwise-healthy IVD may not be appropriate for the regeneration of normal tissue.

For these reasons, many researchers have opted to use stem cells for regeneration of the NP. Stem cells have the unique capacity to generate progeny with the same developmental potential (self-renew) or to differentiate into the lineages of the stem cell’s tissue origin. Stem cells are generally classified as pluripotent (embryonic stem cells [ESCs]) or multipotent (somatic stem cells). Human ESCs are derived from the epiblast cells of a blastocyst. ESCs can be readily grown as undifferentiated cells under defined conditions, providing an unlimited supply of pluripotent stem cells. While they are capable of differentiating into all three germ layers of the embryo – and, hence, all cell types of the human body – there are many ethical issues associated with their acquisition and use. Some examples of these include the controversy of utilizing allogeneic cells for NP tissue engineering, which may result in donor-host rejection as it is controversial as to whether ESCs have immune-privileged properties. In addition, the ability of residual implanted undifferentiated ESCs to form teratomas, an unacceptable complication for a treatment designed for a non-life-threatening disease, is another possibility.

Alternatively, adult somatic stem cells, of which mesenchymal stem cells (MSCs) are one type, may be a more appropriate source of cells. These can differentiate into all cells of mesenchymal lineage and can be readily harvested from a number of tissues, such as bone marrow and fat. Importantly, they can be expanded in culture while retaining their ability to differentiate. For example, studies have verified that human bone marrow MSCs can maintain their chondrogenic differentiation potential up to an approximately 60,000-fold expansion of cell numbers. However, there are some limitations to the use of these cells as their ability to proliferate can decrease with age and disease. Nevertheless, studies have demonstrated the feasibility of using MSCs for regeneration of NP tissue. Le Maître et al. injected human MSCs into bovine NP tissue explants. They found that MSCs from older individuals differentiated spontaneously into chondrocyte-like NP cells upon insertion into NP tissue in vitro. MSCs have also been cultured in chitosan-glycerophosphate hydrogels in vitro. After 4 weeks, the MSCs differentiated into cells with a phenotype that was similar to NP cells; the cells secreted proteoglycans and collagens in a ratio that closely resembles that of NP cells. Autologous MSCs mixed in atelocollagen have been shown to decelerate disc degeneration after implantation into the degenerated discs of rabbits. Transplantation of MSCs alone into animals has also been attempted for in situ regeneration of the NP. Sakai et al. found that injection of MSCs into degenerate rabbit IVDs led to tissue regeneration after 24 weeks. In another study, human MSCs were injected into lumbar discs of pigs either
alone or with a PuraMatrix hydrogel carrier. After 6 months, the injected cells were detected in the disc, confirming their survival; they also expressed typical chondrogenic markers suggesting differentiation toward disc-like cells. The results obtained from the use of MSCs for NP regeneration, while encouraging, are still preliminary. An alternate cell source may be inducible pluripotent stem (iPS) cells, which can be generated by viral transfection of the four transcription factors Oct4, Sox2, c-Myc, and Klf4 (Yamanaka factors) into somatic cells. Human fibroblasts, for example, have been transected successfully. These iPS cells return to an undifferentiated, pluripotent state and are indistinguishable from ESCs in morphology, proliferation, gene expression, and their ability to form teratomas.

Investigation of the specific signalling pathways activated following transfection of the Yamanaka factors have shown that Oct4 and Sox2 are core factors, Klf4 enhances the core factors for development regulation, and c-Myc plays a role in regulating metabolism. These factors were found to regulate at least 14 crucial developmental signalling pathways to maintain ESC pluripotency. In addition, a new technology using virus-independent, transposon-mediated reprogramming of somatic cells into iPS cells has been developed, eliminating one of the potential contraindications to the clinical use of these cells. Although not yet reported, it may be possible to generate iPS cells by transfection of primary NP cells with the Yamanaka factors. This could allow for rapid expansion of a small number of NP cells that would be sufficient for tissue engineering an organ.

Conclusions

Clearly, the development of regenerative medicine for disease treatment is still a long way off. The replacement or regeneration of diseased or damaged tissue with an intact functional tissue generated by the individual’s own cells will be a remarkable feat, and iPS cells represent an exciting advance that moves us one step closer to its realization. The pathologist may have an important role to play in this treatment by providing the appropriate tissue or cells to the tissue engineer.

Acknowledgements

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References

TISSUE ENGINEERING THE NUCLEUS PULPOSUS: IS IT FEASIBLE?


Surgical Pathology Quality Assurance/Quality Improvement in a Community Hospital: A Year in Review

Stanley Todd, MD, Mukund Tinguria, MD, P. Wentworth, MD, A. Croal, MD, Katherine Chorneyko, MD

ABSTRACT
Quality assurance (QA) and quality improvement (QI) programs are mandatory components of virtually all laboratory accreditation processes, with the ultimate purpose of decreasing laboratory errors and increasing patient safety. QA/QI in anatomical pathology encompasses preanalytical, analytical, and postanalytical factors in the areas of cytopathology, histopathology, immunohistochemistry, and surgical and autopsy pathology. Unlike other areas of the laboratory where QA/QI may involve monitoring specific analytes and, in many instances, may be automated, QA/QI in surgical pathology is labour intensive since the gold standard for a “correct” diagnosis is peer review. Although the principles of all surgical pathology QA/QI programs are the same, the application in individual laboratories depends on departmental demographics and other local factors. This review summarizes 1 year (2008) of a surgical pathology QA/QI program in a community hospital setting and addresses some of the challenges in maintaining an active and effective QA/QI program.

RÉSUMÉ

Quality assurance (QA) and quality improvement (QI) initiatives are mandatory components of virtually all laboratory accreditation processes. Furthermore, most laboratories recognize that an organized and active QA/QI program enhances patient safety and minimizes error. There are guidelines and recommendations as to how anatomical pathology QA and QI programs should be structured1–3; however, within these frameworks there is room for flexibility since there is variability in the types of clinical services individual anatomical pathology laboratories...
support, as well as differences in local resources. The analytical aspect of an anatomical pathology QA program encompasses many components including histology, histochemistry, immunohistochemistry, intraoperative consultation, and the final diagnosis or interpretation. The gold standard for “correctness” in diagnostic interpretation is generally considered to be peer review, and many different types of review can and do take place: intradepartmental consultation, external consultation, cancer centre reviews, and the College of Physicians and Surgeons of Ontario Peer Assessment Programme.\textsuperscript{1,4} These activities can be monitored in diverse and innovative ways, and the sharing of how different QA/QI programs are structured is one way to communicate ideas that may be of interest to the anatomical pathology community at large.

The purpose of this review is to provide one example of a surgical pathology QA/QI program in an Ontario community hospital, with a discussion of the challenges faced in implementing such a program.

**Description of a QA Program in Anatomical Pathology**

The Brant Community Healthcare System (BCHS) consists of two sites: the Brantford General Hospital, an acute care facility with 300-plus beds, and Willet Hospital, which provides predominantly outpatient services. The Brantford General Hospital is the regional centre for pediatrics, obstetrics, gynecology, critical care, emergency care, and surgery services. In total, BCHS provides health care services for a population of approximately 120,000 people.

The Anatomical Pathology Department, located at the Brantford General Hospital, handles approximately 8,700 surgical specimens, 2,300 gynecological/nongynecological cytology specimens, and 180 bone marrow aspirates and biopsies per year. This workload is handled by 3.0 full-time equivalent (FTE) pathologists with a support staff of a technical specialist (1.0 FTE), histotechnologists (2.5 FTE), a pathology assistant (1.0 FTE), medical laboratory assistants (1.8 FTE), a cytotechnologist (0.5 FTE), and an administrative assistant. QA/QI monitoring of the technical aspects of histopathology, immunohistochemistry, and hematology are in place as well as interpretative and technical aspects of cytology, but these are not considered in this review.

The surgical pathology QA program was developed in 1997 and involves monthly review of QA benchmarks. One pathologist is the designated QA coordinator, and one clerk is assigned to assist in the administrative aspects of the program. On a monthly basis, they collate statistics using a combination of the hospital laboratory information system (Meditech Client Server) and manual data entry on the following indicators:

- Incomplete requisitions (excluding those that lack a clinical history)
- Specimens inadequate for diagnosis
- Intraoperative consultations (agreement with permanent, disagreement with permanent, deferred cases)
- Internal consultations
- External consultations (including cancer centre reviews and cases sent for second opinion)
- Peer-reviewed cases
- Corrected or revised reports (apart from those resulting from cancer centre reviews or second opinions)
- Supplementary reports (e.g., ER/PR results, findings following decalcification, additional information from histochemistry/immunohistochemistry or consultation)

In addition, a retrospective, monthly peer review of approximately 25 cases is done. This review is semitargeted in the sense that cases with a low likelihood of error such as hernia sacs or vas deferens are not reviewed. Cases that have already been subject to an internal or external consultation are also not selected. An administrative assistant, who has been instructed as to which cases are appropriate for review, selects the cases and organizes the paperwork and slides. The pathologists review the cases under the following criteria:

- Adequacy of clinical history
- Gross description
- Microscopic description
- Ancillary studies
- Diagnosis
- Turnaround time
Discrepant diagnoses are qualified as to minor (no impact on patient care or management) or major (with impact on patient care or management, or a significant change in diagnosis even with no clinical impact). All discrepancies are discussed with the original pathologist, and a decision is made regarding the appropriate course of action. In some instances, an additional external consultation may be undertaken. If necessary, the clinician is contacted directly and a corrected report is issued.

On a monthly basis, the QA statistics are presented to the hospital Medical Quality Improvement Committee. This committee considers all aspects of quality of care in the hospital and has representation from all departments as well as the Risk and Quality Management Department. All discrepant diagnoses identified either by peer review or external review are disclosed, with the course of action. Incident reports, which are generated for errors arising from nonprofessional actions (e.g., specimen mislabeling), are tracked in a hospital-wide electronic patient safety system (Risk Monitor Pro Safety Reporting System) and are monitored by risk management, which reports to the Medical Quality Improvement Committee.

Summary of 2008 Statistics

In 2008, three full-time pathologists handled the following workload: 8,652 surgical pathology cases, 180 bone marrow aspirates and biopsies, 58 peripheral smear interpretations, 1,221 gynecological cytology cases, 1,142 non-gynecological cytology cases, 90 semen analyses, and 78 autopsies.

With regard to tracking of incomplete requisitions and inadequate specimens, a total of 649 of 8,652 cases had incomplete requisitions (7.5%). These represent specimens that could not be accessioned at the time of specimen receipt due to incomplete patient or specimen data (not including incomplete clinical history). Monthly tracking of incomplete requisitions shows that there is monthly variability ranging from 4 to 11% (Table 1). Specimens were considered inadequate for diagnosis if there was insufficient cellular material or another reason for which a specimen could not be interpreted, for example, extensive cautery artifact. Overall, in 2008 less than 1% (monthly range 0.3–1.4%) of the specimens fell into this category.

Table 1. Incomplete Requisitions and Inadequate Specimens, Brant Community Healthcare System, 2008

<table>
<thead>
<tr>
<th>Month</th>
<th>No. of Surgical Cases</th>
<th>No. of Incomplete Requisitions (%)</th>
<th>No. of Cases Inadequate for Diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>709</td>
<td>57 (7)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>February</td>
<td>720</td>
<td>74 (10)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>March</td>
<td>552</td>
<td>37 (7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>April</td>
<td>852</td>
<td>54 (6)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>May</td>
<td>742</td>
<td>26 (4)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>June</td>
<td>789</td>
<td>73 (9)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>July</td>
<td>772</td>
<td>87 (11)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>August</td>
<td>538</td>
<td>49 (9)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>September</td>
<td>764</td>
<td>65 (9)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>October</td>
<td>846</td>
<td>56 (7)</td>
<td>12 (1.4)</td>
</tr>
<tr>
<td>November</td>
<td>727</td>
<td>41 (6)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>December</td>
<td>641</td>
<td>30 (5)</td>
<td>5 (0.8)</td>
</tr>
</tbody>
</table>

Intraoperative consultation was requested in 18 cases, and in 15 there was agreement with the final surgical diagnosis (83%). In two cases the diagnosis was deferred, and in one case there was a disagreement with the final surgical diagnosis due to sampling (an ovarian cyst diagnosed as benign mucinous cystadenoma on frozen section and borderline mucinous tumour on permanent sections).

In 2008, a total of 12.7% of cases were seen by two or more pathologists (internal consultations, external consultations, and peer review). Internal consultations were more numerous than external consultations, except in the summer month of July (Figure 1). In 2008, 7% of cases were reviewed as internal consultations, while 4% were reviewed as external consultations or were subject to external review (cancer centre or other requested reviews). In total, there were 300 (3.5%) semitargeted peer-reviewed cases, 595 (6.9%) internal consultations, and 311 (3.6%) external consultations. In some instances, internal consultations were also referred for external review. Peer review detected nine discrepancies (four minor and five major), representing 0.1% of the 2008 cases. Cases sent for external consultation are considered preliminary or deferred diagnoses until the second opinion has been received and, as such, are not
considered discrepant. Discrepancies from cancer centre reviews were also monitored and documented. No major or minor discrepancies were identified in these latter reviews. For any significant discrepancies, clinicians are contacted and corrected reports are issued. Reports corrected for other reasons (not part of the external or peer-review process) are monitored; in 2008, five corrected or revised reports were issued in this category. Supplementary reports, in which additional information from ancillary tests, external consultations, or decalcification was provided, were issued in 196 cases (2.3%).

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Discussion

In the wake of three major public inquires into errors in anatomical pathology, as well as the current atmosphere of increasing case complexity, it is important for an anatomical pathology service to have a robust QA/QI program. However, a comprehensive and effective program becomes more difficult to administer as workload complexity increases and budget constraints continue. The program at BCHS is one example of a community health care QA/QI program that monitors specific preanalytical, analytical, and postanalytical factors on a monthly basis. Although specific aspects of QA programs have been published in the literature – for example, specimen labelling errors, frozen section/permanent section monitoring, and second reviews – there are very few publications outlining the components of a QA/QI program in an individual hospital. In 1998, a 5-year review of the internal QA program in a tertiary care teaching hospital in Australia was summarized; however, to our knowledge, there is no published review of a community hospital QA/QI program. Regular monitoring of indicators can reaffirm that an anatomical pathology service is functioning well and, in addition, can identify specific targets for possible intervention or education. For example, incomplete requisitions are a problem as they require laboratory staff to spend time sorting out the deficiencies. This causes delays in accessioning of cases and diverts laboratory staff from other duties. The monitoring of incomplete requisitions as part of the BCHS QA/QI program identified continued deficiencies in this area, and it was targeted as an area for improvement. This has been followed up by the organization of short, in-service education sessions about this topic to clinical areas in which specimens are procured. Continued monitoring of incomplete requisitions will show if this intervention has been successful.

The success of any QA program is measured by improved patient safety through a decreased error rate. A review of the QA program at BCHS shows that although errors are very low (<1%), they can occur. One challenge faced by this department is to ensure timely identification and correction of errors. The peer-review process occurs 1 month following sign out; while this is within a reasonable time frame, ideally it should be shortened. Prospective peer review would be preferable since errors would be corrected before the release of a case; however, workload and staffing resources limit the ability to provide this type of QA/QI. It should be noted that, as in most departments, many cases are shown to other pathologists as internal departmental consultations, which is a form of prospective peer review. Nonetheless, it is hoped that with continued discussion of resources, a prospective QA process can be implemented.

As health care becomes more complex and fiscal constraints
continue, the main challenge in realizing an effective QA/QI program is resources. Although in BCHS there is administrative and technical support, as service workload increases it is more difficult for support staff to find time to gather paperwork, collate statistics, and pull slides. For the pathologists, increasing work volumes and complexity coupled with other service duties as well as multidisciplinary round preparation, committee work, other QA activities, and continuing medical education requirements make it challenging to complete the peer-review process in a timely fashion. Furthermore, when the review is semitargeted so that complex and critical cases are largely assessed, more time is required than if only simple cases were targeted. Therefore, in any consideration of departmental workload, not only the number of QA cases reviewed but also their complexity must be taken into account.

Unlike larger community hospitals or academic departments, a medical staff of only three pathologists faces the challenge of a limited pool of individuals for peer review. Across Canada, there are smaller, and occasionally solo, pathology practices, which would make implementation of a QA/QI even more challenging. There may be opportunities for larger centres to provide support for smaller ones as long as there are adequate resources to do so. Virtual microscopy will likely be important in future QA/QI initiatives of this sort.12–14

Conclusion
A QA/QI program in anatomical pathology is an organized, dynamic ongoing activity that enhances patient safety and minimizes error. Although other laboratories in Canada will have similar but individual QA/QI programs, they all may face the same challenges in regard to resources and implementation. Increased attention to resources for anatomical pathology QA/QI initiatives is imperative to maintain the high quality of anatomical pathology services in Canada.

Acknowledgements
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References
Kulcsar Lecture 2009: Highlights from the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference

Manon Auger, MD, FRCP(C)

ABSTRACT
The National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference provides a framework of guidelines on the indications, pre-fine-needle aspiration requirements, training, techniques, diagnostic terminology, use of ancillary studies, and post-fine-needle aspiration testing and treatment options for thyroid fine-needle aspirates. This article is a synopsis of those guidelines, presented as the Kulcsar Lecture for the Canadian Society of Cytology symposium at the annual meeting of the Canadian Association of Pathologists in 2009.

Résumé
La Conférence sur l'état de la science quant à la biopsie de la thyroïde par aspiration à l'aiguille du National Cancer Institute a donné lieu à l'élaboration d’un cadre de référence de lignes directrices sur les indications, les critères préalables, la formation, les techniques, la terminologie diagnostique, les études connexes, les épreuves subséquentes et les options thérapeutiques selon la nature de l’aspirat. L’article, qui expose l’essentiel de ces lignes directrices, reprend la conférence Kulcsar présentée au symposium de la Société canadienne de cytopathologie lors du congrès annuel de l’Association canadienne des pathologistes en 2009.

It is an honour for me to present the Kulcsar Lecture, which was instituted in 1990 and has since been given annually to the Canadian Society of Cytology (CSC) in memory of Dr. David D. Kulcsar. Dr. Kulcsar played a primordial role in the development of the CSC as one of the founding members of the Canadian Cytopathology Council (CCC), later renamed CSC. He was the first secretary-treasurer of the CCC/CSC from 1961 to 1966 and the editor of the CCC newsletter; he became chair of the CSC in 1967–1968. Interestingly, Dr. Kulcsar, along with Drs. Donald W. Thompson and George H. Anderson, was involved in an early survey of cytopathology laboratories across Canada in 1967. The only nongynecological specimens specifically mentioned in their report were pulmonary, gastric, urinary, and serous effusions; all the others were are grouped under the “miscellaneous” category, presumably including a small number of thyroid fine-needle aspirations (FNAs). This underscores the evolution in the practice of cytopathology over the past 40 years, with thyroid FNAs now representing one of the most common nongynecological specimens encountered in many cytopathology laboratories. This change stems from a combination of factors, including the fact that thyroid nodules are very common and are found in approximately 4–7% of the adult population. Because most are benign, surgery for all thyroid nodules is not appropriate, and FNA is now recognized as the most accurate and cost-effective method for evaluating thyroid nodules. One problematic aspect of thyroid FNAs is that pathologists differ widely in how they report them. This proliferation of
reporting formats has made it difficult to compare data for parameters such as sensitivity, specificity, and positive and negative predictive values between centres, and is confusing for clinicians to interpret reports. This variability is best documented in Helen Wang’s review of the published literature (87 publications between 1966 and December 2004) on thyroid FNA reporting: she documents at least 17 different schemes for reporting thyroid FNA results, ranging from simplistic two-category schemes (i.e., benign versus suspicious/malignant, corresponding to the clinically relevant decision making of surgical versus nonsurgical follow-up) to six or more schemes containing one or more layers of uncertainty between benign and malignant. Although there have been attempts at standardization of thyroid FNA reporting over the years, by the Papanicolaou Society of Cytopathology Task Force and the American Association of Clinical Endocrinologists among others, none has been widely accepted.

In light of the above, the National Cancer Institute (NCI), under the initiative of Dr. Andrea Abati, sponsored the Thyroid FNA: State of the Science Conference, which was held on October 22–23, 2007, in Bethesda, Maryland. The conference was prefaced by an online web-based bulletin board discussion between May 1 and August 15, 2007. Six committees were appointed, consisting of recognized experts in the field of thyroid, including cytopathologists, surgical pathologists, endocrinologists, surgeons, and radiologists. The goal of the conference was to encourage interdisciplinary dialogue and education regarding the evaluation, management, and interpretative reporting of thyroid nodules. The discussions at the 2-day “live” conference were efficiently and tactfully co-moderated by Drs. Edmund S. Cibas, a cytopathologist, and Susan J. Mandel, an endocrinologist, both well respected in the field of thyroid diseases.

This synopsis addresses only selected highlights from the NCI conference; detailed reviews on this topic are available. At the time of this writing, a comprehensive atlas edited by Drs. Edmund Cibas and Syed Ali, related to each of the diagnostic categories endorsed at the NCI conference, was to be published in the fall of 2009, followed by an online atlas.

**Indications for Thyroid FNA and Pre-FNA Requirements**

The indications for performing an FNA of a thyroid nodule depend on the diagnostic modality used to discover the nodule, that is, palpation versus imaging. With the increased use of imaging, thyroid nodules are now more frequently incidental findings during workup for other medical problems, as opposed to usually discovered by palpation a few years ago.

**Nodules Discovered by Palpation**

Because most nodules discovered by palpation measure ≥1 cm, they are considered clinically significant and deserving of further evaluation. A clinical history, physical examination, especially of the thyroid and neck lymph nodes, and thyroid-stimulating hormone (TSH) measurements should be performed. If the TSH is normal or high, then dedicated thyroid ultrasound (US) imaging should be performed. If the TSH is suppressed (<0.1 mIU/L), a radionuclide thyroid scan should be performed. If the latter reveals a functioning nodule, an FNA is not required because the risk of malignancy is very low; if the nodule is isofunctional or hypofunctional, further assessment by a dedicated thyroid ultrasonography is warranted to determine the need for an FNA.

**Nodules Discovered by Imaging**

Nodules discovered by imaging may require FNA depending on their size and on the type of imaging technique performed. If the uptake within the thyroid on a positron emission tomography (PET) scan is focal (rather than diffuse), an FNA is indicated as these nodules have a relatively high rate of malignancy (14–50%). In contrast, if the uptake is diffuse, an FNA is not needed unless thyroid ultrasonography shows a discrete nodule. Similarly, a “hot” thyroid nodule on a sestamibi scan that is confirmed by ultrasonography to be a discrete nodule should be aspirated because the risk of malignancy ranges between 22 and 66%. If discovered by computed tomography (CT) or magnetic resonance imaging (MRI), FNA is only required if a dedicated thyroid ultrasonography shows suspicious features. For nodules discovered by ultrasonography in the general head and neck area, a dedicated thyroid ultrasonography is recommended.
In general, nodules with a maximal diameter >1–1.5 cm should undergo FNA unless they are a simple cyst or a septate cyst without a solid component; alternatively, they can be followed up at 6- to 18-month intervals if there are no suspicious features by ultrasonography. If the nodules are <1 cm diameter, an FNA should be considered if suspicious ultrasonographic features are present, although a consensus is lacking on how to deal with these.

What are the ultrasonographic features considered suspicious in thyroid lesions? They include irregular or lobulated margins, microcalcifications, hypoechoic solid nodules, intranodular vascularity, a taller-than-wide shape, signs of spread beyond the capsule of the nodule, and nodal metastases.

**US- versus Palpation-Guided FNA**

When should a thyroid FNA be performed by ultrasonography versus palpation? In many cases, either approach is acceptable. Because recent guidelines from the American Thyroid Association recommend that all patients with palpable nodules undergo a dedicated thyroid US examination, an increasing number of FNAs are being done by US guidance. Ultrasonography provides precise information regarding the location, size, and structure (cystic versus solid) of the lesion. In addition, published data indicate that US guidance reduces the rate of nondiagnostic and of false-negative specimens. Nevertheless, palpation-guided FNA is still worthwhile. It has been performed with a high rate of success over the years, is less costly, and is more convenient. It is the preferred method where health care resources are limited.

The circumstances when an US-guided FNA would be preferred, if available, include (1) a diffusely enlarged thyroid with no discrete nodule on physical examination, (2) a poorly palpable nodule, (3) a predominantly cystic nodule (>25%), (4) a small nodule (<1 cm), and (5) a prior nondiagnostic FNA.

**Pre-FNA Requirements**

The pre-FNA requirements relate to the informed consent and the requisition form accompanying the thyroid FNA specimen. The informed consent must include the following: a description of procedure, a listing of potential risks and complications, a mention of the possibility of nondiagnostic results and of the potential need for re-biopsy, and the patient’s identifying information (name and address of person requesting test, name or unique identifier, gender, age or birth date, name of test to be performed, specimen source, and date of specimen collection). The minimal clinical information required on the requisition for thyroid FNA should include the following: (1) the exact location of the nodule (allowing correlation with the ultrasonographic findings); (2) the size of the nodule (greatest dimension); (3) a history of hypothyroidism or autoimmune thyroiditis, a positive antithyroid antibody test, Graves’ disease, or iodine 131 (I131) or external beam radiation therapy; and (4) a personal history of cancer (including cancer of other body sites) and family history of thyroid cancer. All these factors can influence the interpretation of a thyroid FNA because they suggest situations that change the expectations for a specific morphological pattern or for the probability of cancer. For example, while low serum TSH levels are associated with a lower risk of thyroid carcinoma, cellular changes associated with I131 therapy, external beam radiation, a prior FNA, autoimmune thyroiditis, and Graves’ disease are all known causes of false-positive diagnoses.

**Thyroid FNA Training**

Training for the performance of thyroid FNA is critical because the majority of diagnostic failures are due to nondiagnostic samples or to pathologists issuing diagnoses on samples with inadequate material. Suggested components of an FNA training program include, but are not restricted to, studying an illustrated text or other teaching aid on the technique, viewing a detailed instructional video (such as those by Dr. Britt-Marie Ljung, available on www.papsociety.org/fna/html, performing bench practice (e.g., on bovine liver, or even on tomatoes and oranges!), and, finally, performing actual sampling of thyroid nodules under supervision. No specific number of FNAs is stipulated to reach proficiency.

**Thyroid FNA Techniques**

Thyroid FNAs are best performed using 25- or 27-gauge needles to minimize bleeding and pain; 22- or 23-gauge needles were previously used in some facilities.
needles should be reserved for only drainage of the contents of viscous colloid cysts. The technique can be successfully performed using a needle alone, or with a syringe, with or without a pencil- or pistol-type syringe holder, depending on the preference of the aspirator. Local anesthesia usually is not needed unless the patient is particularly anxious.

Thyroid FNA material for routine examination is best handled by making direct smears on glass slides; these can be air-dried for Romanovsky’s stain and/or spray-fixed or wet-fixed in 95% alcohol for Papanicolaou’s stain. Other preparatory options include cytopsins, liquid-based cytology, and cell blocks for tissue fragments as needed. If resources permit, immediate on-site evaluation is helpful for the assessment of specimen adequacy and for triaging specimens for ancillary studies. If immediate assessment is available, the sampling can stop when (1) a cyst is completely drained and there is no residual mass, (2) a specific malignancy is identified, or (3) the aspirate appears adequate. Conversely, sampling should continue when (1) a residual mass remains after a cyst is completely drained, (2) the cellularity of the initial passes is inadequate, or (3) the enrichment of a sample for a cell block or ancillary studies is needed. If no on-site assessment is available, a reasonable number of passes (two to five) from different sites is recommended, with representative tissue from each pass smeared on a slide and the remaining tissue rinsed into a collection tube with transport fluid.

Of note, core biopsy of thyroid has failed to gain widespread acceptance because of its small but definite risk of complications (e.g., bleeding, nerve injury, tracheal perforation, and tumour transplantation) compared with FNAs. In addition, the differential diagnosis of benign versus malignant follicular lesions is usually impossible on core biopsies, and, most importantly, the nuclear features of papillary carcinoma are more difficult to appreciate than in FNAs. Therefore, FNA remains the best technique for the initial investigation of thyroid nodules.

### Diagnostic Terminology and Morphological Criteria

The NCI diagnostic classification of thyroid lesions in FNA specimens includes six categories: benign, follicular neoplasm (specify if Hürthle cell neoplasm), atypia of undetermined significance, suspicious, malignant, and nondiagnostic. This classification is based on a risk of malignancy for each category (Table 1).

<table>
<thead>
<tr>
<th>Diagnostic Categories</th>
<th>Alternate Acceptable Terminology</th>
<th>Risk of Malignancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
<td>0–3</td>
</tr>
<tr>
<td>Atypia of undetermined significance</td>
<td>Atypical follicular lesions</td>
<td>5–15</td>
</tr>
<tr>
<td></td>
<td>Cellular follicular lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indeterminate follicular lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R/O neoplasm</td>
<td></td>
</tr>
<tr>
<td>Follicular neoplasm (specify if Hürthle)</td>
<td>Suspicious for neoplasm</td>
<td>15–30</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td></td>
<td>60–75</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td>97–99</td>
</tr>
<tr>
<td>Nondiagnostic</td>
<td>Unsatisfactory</td>
<td></td>
</tr>
</tbody>
</table>

*FNA = fine-needle aspiration; R/O = rule out.*
Adequacy, Colloid Nodules, and Cysts

The first decision to be taken before evaluating a thyroid FNA is to decide if it is adequate or not. This topic is controversial, and opinions have differed over the years. NCI recommends that all thyroid FNAs must be technically adequate, with well-preserved and well-prepared thyroid follicular epithelial cells for interpretation; at least six clusters of at least 10 follicular cells must be present to ensure adequacy. The term nondiagnostic (synonyms: unsatisfactory, inadequate, and insufficient) should be reserved for specimens of limited cellularity, containing no follicular epithelium, or of poor preservation precluding cellular evaluation.

Exceptions to the adequacy requirements can be made in the following circumstances: (1) any specimen with any atypical features cannot be called nondiagnostic or unsatisfactory and should be placed in the “atypical” category; (2) cases of lymphocytic thyroiditis, because they may occasionally yield only lymphocytes with few follicular cells; and (3) FNAs containing abundant thick colloid (i.e., slide full of colloid) and little else. This latter exception was one of the “hot topics” at the NCI conference and generated a long discussion with many different views expressed. In the end, it was decided that because an FNA containing abundant colloid and little else most likely represents a colloid nodule and carries an insignificant risk of malignancy, it can be included in the benign category as being “suggestive of colloid nodule.”

Another hot topic at the NCI conference was the question of how to categorize FNAs containing only (or mostly) macrophages; that is, whether to place them in the benign versus the nondiagnostic versus their own category. Simple, noncomplex cysts carry a risk of malignancy of 1–4%, whereas mixed (solid and cystic nodules), large (>3 cm), and recurring cysts carry a risk of malignancy of up to 14%. Therefore, in view of the fact that a small but significant percentage of cystic specimens may represent sampling from a cystic papillary thyroid carcinoma (PTC), it was decided that reassurance with a “benign” category would be inappropriate. The conclusion was that cystic specimens containing macrophages only (or macrophages with less than six groups of follicular cells) should be diagnosed as nondiagnostic/insufficient for diagnosis: cyst fluid only with a recommendation that correlation should be made with the ultrasonographic findings; an optional disclaimer that “cystic PTC cannot be excluded” may be added (Figure 1).

A detailed description of the morphological criteria of each diagnostic category is beyond the scope of this synopsis; only selected topics are covered.

Benign

The general category benign consists mostly of nodular goitre, hyperplastic/adenomatoid nodule, colloid nodule, chronic lymphocytic thyroiditis (Hashimoto’s thyroiditis), and granulomatous thyroiditis. The benign category carries a very low risk of malignancy. In general, the non-thyroiditis lesions are characterized by a predominantly honeycomb or macrofollicular arrangement of follicular cells (a circular formation composed of >15 follicular cells that are evenly spaced) (Figure 2).
Figure 2. Thyroid fine-needle aspiration of nodular goitre. The macrofollicular configuration of the follicular cells can also produce a honeycomb arrangement upon flattening of the follicular spheres when spread on to a slide. This pattern usually connotes a non-neoplastic/benign process. The histological follow-up in this case was nodular hyperplasia/nodular goitre. (Papanicolaou’s stain, original magnification 100x)

Follicular Neoplasms (Specify if Hürthle Cell Neoplasms)
The diagnostic category follicular neoplasm applies to non-papillary follicular-patterned neoplasms, including Hürthle cell neoplasms. This category carries an intermediate risk of malignancy. Many terms have been used in the past for follicular neoplasms, including microfollicular proliferation/lesion, suggestive of neoplasm, follicular lesion, and suspicious for follicular neoplasm; of those, only the latter term is still acceptable as alternate wording in lieu of follicular neoplasm.

In general, specimens falling into this category should be hypercellular and characterized by follicular cells arranged in a predominantly syncytial or microfollicular pattern (a circular formation composed of six to 15 follicular cells) and/or trabeculae (cords), with scant colloid (Figure 3). The nuclear features of PTC should be absent. The distinction between follicular adenoma and follicular carcinoma cannot be made on cytology.

Hürthle cell neoplasms are also characterized by hypercellularity and a predominant syncytial, microfollicular pattern and/or trabeculae (cords) (of Hürthle cells) with scant colloid. In contrast to most follicular neoplasms, Hürthle cell neoplasms tend to exhibit more single/dyscohesive cells. There is usually a pure population of Hürthle cells, and these typically exhibit prominent nucleoli, whereas Hürthle cells in non-neoplastic lesions usually have inconspicuous or absent nucleoli. As is the case for follicular neoplasms, the distinction between Hürthle cell adenoma and Hürthle cell carcinoma cannot be made on cytology.

Atypia of Undetermined Significance
The term atypia of undetermined significance (AUS) represents a heterogeneous category of cases and should be reserved for cases exhibiting cytological findings that are not convincingly benign, yet the degree of cellular or architectural atypia is not sufficient for an interpretation of follicular/Hürthle cell neoplasm or suspicious for...
malignancy. This category should represent <7% of all thyroid FNAs, and the risk of malignancy should be in the range of 5–15%.

Some cases fall into the AUS category because they correspond to compromised specimens due to low cellularity, poor fixation, or obscuring blood. Other types of cases falling into this category include the following:

- Atypical follicular lesion of undetermined significance (FLUS) – that is, follicular lesions between benign and follicular neoplasms, for example, with mixed micro- and macrofollicular patterns but without predominance of either
- Atypical Hürthle cell lesion of undetermined significance (HUS) – Hürthle cell lesions between benign and Hürthle cell neoplasms, for example, monotonous Hürthle cell population but without other features of Hürthle cell neoplasm
- Atypical cells present, cannot rule out PTC – some concern about PTC but insufficient to be diagnosed as “suspicious”
- Other nonspecific changes that cause concern; these should be specified in the diagnosis, for example, atypical cyst-lining cells

In summary, cases falling into the AUS category do so based on architectural atypia, cytological atypia, or a compromised specimen. As with atypical squamous cells in gynecological cytology when this term was first introduced into the diagnostic scheme, the new category AUS will require more rigorously defined morphological criteria. The publication of the atlas on thyroid FNA cytology edited by Drs. Edmund Cibas and Syed Ali will certainly help its application in daily practice.

**Suspicious for Malignancy**

The term suspicious for malignancy should be used when the cytological findings are suggestive but insufficient, for either qualitative or quantitative reasons, for a definitive diagnosis of malignancy. The subtype of the suspected malignancy should be specified whenever possible. The cases fall into the following subcategories: (1) suspicious for PTC (a majority of those, 50–75%, turn out to be follicular variant of PTC), (2) suspicious for medullary carcinoma, (3) suspicious for other primary or secondary malignancy, or (4) suspicious for neoplasm because of total necrosis of lesional cells.

![Figure 4. Thyroid fine-needle aspiration of papillary thyroid carcinoma. A, Subtle syncytial arrangement of the follicular cells exhibiting numerous nuclear grooves (“coffee-bean” appearance), with fine, powdery chromatin and micronucleoli. (Papanicolaou’s stain, original magnification 400x) B, Characteristic nuclear features of papillary thyroid carcinoma with the oval nuclei, fine chromatin, nuclear grooves, micronucleoli, and intranuclear inclusions. (Papanicolaou’s stain, original magnification 600x).](image-url)
Malignant

The category *malignant* should be used whenever the cytological features are diagnostic of malignancy; the type of malignancy should be specified. Cases therefore fall into the following subcategories: (1) PTC (Figure 4), (2) medullary carcinoma, (3) anaplastic carcinoma, or (4) metastatic carcinoma or other malignancy.

Utilization of Ancillary Studies in Thyroid FNA

Ancillary studies can be performed on thyroid FNA specimens, most commonly immunocytochemistry (usually on cell block material; less often on smears, cytospins, or liquid-based preparations). The most frequent applications relate to the diagnoses of medullary thyroid carcinoma and anaplastic carcinoma and, rarely, suspected metastasis to the thyroid.

A suspected diagnosis of medullary thyroid carcinoma can be confirmed by positive staining of the cells for calcitonin, carcinoembryonic antigen (CEA), synaptophysin, CD56, and chromogranin, with a negative thyroglobulin stain. Findings can be correlated with serum calcitonin. The negative staining for thyroglobulin distinguishes medullary carcinoma from neoplasms derived from follicular epithelium. For example, Hürthle cell neoplasms share several cytological features (e.g., eccentric nuclei, binucleation, and multinucleation) with medullary carcinomas but, in contrast to the latter, Hürthle cell neoplasms should be positive for thyroglobulin and negative for calcitonin, chromogranin, and CEA. Of note, thyroid transcription factor 1 (TTF-1) is not helpful in this differential diagnosis because both medullary carcinoma and follicular-derived neoplasms express this marker.

Immunocytochemistry can also be attempted to differentiate anaplastic thyroid carcinoma from metastatic carcinoma; however, it is often not useful because most anaplastic thyroid carcinomas lose specific thyroid markers. However, if focal expression of thyroglobulin and/or TTF-1 is seen in the context of an anaplastic malignancy, it would support a diagnosis of anaplastic thyroid carcinoma. Distinguishing parathyroid from thyroid follicular-pattern lesions can be very difficult on purely cytological features, and immunocytochemistry for TTF-1, parathyroid hormone (PTH), and chromogranin may be useful in this context; parathyroid lesions should be positive for chromogranin and PTH but negative for TTF-1.

Flow cytometry may be used in thyroid FNA when lymphoma is suspected. However, because clonal B-cell lymphoid populations may be detected in the context of Hashimoto’s thyroiditis without concomitant lymphoma, caution must be exercised when interpreting flow cytometry results. The indication for flow cytometric analysis should therefore be based on cytomorphological or clinical features that raise the suspicion of lymphoma; it should not be used routinely when lymphoid material is obtained in thyroid FNAs. Likewise, immunophenotyping results from thyroid FNA samples should be interpreted with caution since Hashimoto’s thyroiditis may yield kappa/lambda light chain ratios that are skewed beyond the normal values associated with reactive lymphoid lesions.

The use of ancillary studies to reclassify an indeterminate or suspicious FNA into a benign or malignant category or to refine the risk of malignancy within this category is controversial. Although touted as potential markers for reclassifying indeterminate or suspicious FNAs, immunocytochemical markers (e.g., galectin-3, cytokeratin 19, and HBME-1) and the identification of chromosomal translocations (RET/PTC, PAX8/PPARG) or of genetic mutations (BRAF, RAS) are not recommended at this time for widespread clinical use due to insufficient evidence.

Post-FNA Testing and Treatment Options

Follow-Up of Nondiagnostic FNA Results

There is no universally accepted approach for the follow-up of nondiagnostic FNA results. If the lesion is cystic (i.e., consisting of blood and histiocytes without follicular epithelium), it requires correlation with ultrasonographic findings. If the ultrasonographic features indicate a low risk of malignancy, the best approach is nonsurgical follow-up with repeat FNAs at 6- to 18-month intervals. If the ultrasonographic features are suspicious, a repeat FNA with US-guidance (with on-site assessment if possible) is recommended. If the repeat FNA is still nondiagnostic, close clinical and ultrasonographic follow-up is appropriate.

If solid, a repeat FNA with US guidance (with on-site assessment if possible) should be done. If the repeat FNA is still nondiagnostic, surgery should be considered as the risk
of malignancy is approximately 9%. However, close clinical and ultrasonographic follow-up is a reasonable alternative to surgery, particularly if the patient is reliable. When growth of the nodule is detected during US surveillance, a repeat FNA should preferably be performed; alternatively, the nodule can be excised. In general, the interval between FNAs should not be less than 3 months to avoid the pitfalls of reparative changes.

Follow-Up of Benign FNA Results
Because the false-negative rate of benign FNA results is low but not insignificant, careful clinical follow-up is recommended. If the nodule is easily palpable, clinical follow-up by physical examination at 6–18 months is suggested; if it is not easily palpable, then follow-up should include an US examination at 6–18 months. The same approach is recommended regardless of the number of nodules as the risk of malignancy is the same in both situations. If suspicious features are seen on ultrasonography, more frequent clinical and ultrasonographic follow-ups are recommended. Because the false-negative rate may be higher in palpation-directed FNA than in US-guided FNA, closer follow-up is required when FNAs are performed with palpation. Of note, thyroxine (T₄)- suppression therapy is no longer recommended under these circumstances.

If significant growth of the nodule(s) is detected (a 20% increase in diameter or a minimum 2 mm increase in two dimensions), either by palpation or ultrasonography, or if a change of ultrasonographic features occurs on follow-up, a repeat FNA or surgical excision can be considered. The total duration of the follow-up for benign FNA results should be at least 3–5 years. Repeat FNA may be done under ultrasonography, with immediate assessment of adequacy, if possible. Alcohol ablation may be considered in select patients who have predominantly cystic and cytologically benign nodules.

Follow-Up of Atypia of Undetermined Significance
Because of the variation in criteria to date, the reported prevalence rates of malignancy for this category have been variable. Ninety to 95% of AUS cases represent adenomas or dominant nodules in goitres, while approximately 5–15% turn out to malignant. In general, the committee concluded that a conservative approach should be adopted for atypical thyroid FNAs. The majority of these lesions should be re-aspirated at 3–6 months in an attempt to define them more clearly. If the repeat FNA remains atypical, surgical consultation should be contemplated. Also, an expert cytopathology consultation may be considered for an initial FNA diagnosis of AUS.

Follow-Up of an FNA with the Diagnosis “Neoplasm”
The follow-up of an FNA with a diagnosis of neoplasm is surgical exploration, usually a lobectomy. Frozen section is not recommended for assessment of capsular invasion. If the surgical excision shows a follicular carcinoma or the follicular variant of PTC, a complete thyroidectomy is usually performed; however, a lobectomy may be sufficient for small, minimally invasive tumours.

Follow-Up of an FNA with the Diagnosis “Suspicious for Malignancy”
Because 50–75% of the FNA cases diagnosed as suspicious for malignancy turn out to be PTC, the appropriate action is surgical consultation.

Follow-Up of an FNA with the Diagnosis “Malignant”
The follow-up of an FNA diagnosed as malignant is surgical, unless clinically contraindicated, for example, in metastatic cancer.

Conclusion
The NCI Thyroid FNA State of the Science Conference was a very successful interdisciplinary educational forum on the evaluation, interpretation, and reporting of thyroid FNAs. The standardized reporting terminology, if adopted, should ultimately translate into improved patient diagnosis and care.

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The activities outlined below are indicative of the services required by the CAP for this position.

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The Consultant is engaged as an independent Consultant providing services to the Canadian Association of Pathologists (CAP), and is not engaged as an employee or agent of the Canadian Association of Pathologists.

**Qualifications**
- Proficient in a variety of computer applications including use of data processing and bookkeeping
- Excellent oral, written, analytical and technical skills
- Experience in formulating educational objectives goals and programs
- Ability to work closely with professionals and internal and external partners
- Bookkeeping and management of funds flowing through this initiative
- Ability to manage data in a reliable manner with easy retrieval
- Ability to multitask and to function independently as, and when, necessary
- Strong organizational and planning skills
- Background in journalism would be an asset

Each project will have a detailed comprehensive statement of the objectives and needs required, including timelines and deliverables. A work plan will be constructed according to the project requirements.

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To apply for this position, please forward your résumé, covering letter and salary expectations, by January 29, 2010, via electronic address: cap@rcpsc.edu

Dr. Joan Sweet, Chair of the Search Committee, Canadian Association of Pathologists - 774 Echo Drive, Ottawa, ON K1S 5N8

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We thank all applicants for their interest; however, only those under consideration will be contacted.
Forensic Pathologist
Hamilton Regional Laboratory Medicine Program
and McMaster University
Hamilton, Ontario

Applications are invited for a full-time Forensic Pathologist position with the Hamilton Regional Laboratory Medicine Program (HRLMP). The Forensic Pathology Unit is a sub-specialty of the Anatomic Pathology section of the HRLMP and is geographically located at the General Hospital site of Hamilton Health Sciences. The Unit has two full-time Forensic Pathologists, with faculty appointments in the Department of Pathology and Molecular Medicine, McMaster University. As part of our Academic Health Sciences Centre, support is available from other branches of laboratory medicine including in-house consultation with neuropathology and cardiovascular pathology. Pediatric and other sub-specialty pathologists are readily available for consultation.

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The successful candidate is expected to teach undergraduate and medical students, residents in pathology and clinical programs, as well as representatives of law enforcement agencies and the judiciary. In anticipation of the Royal College of Physicians & Surgeons of Canada (RCPSC) approval of an accredited forensic pathology fellowship program, full participation in teaching such trainees is mandatory. Research is highly encouraged and expected. Interested candidates should have RCPSC Specialty certification or equivalent in either Anatomic or General Pathology, with additional training in Forensic Pathology, and be eligible for medical licensure in Ontario. The individual will be required to pass the RCPSC subspecialty examination in forensic pathology within two years of appointment.

Interested candidates are invited to submit a cover letter, curriculum vitae and the names and addresses of three referees by December 31, 2009 to:
Dr. Vina Alexopoulou
Director, Anatomical Pathology, and Deputy Chief, Hamilton Regional Laboratory Medicine Program
Professor of Pathology and Molecular Medicine
McMaster University, HSC 2N19
1200 Main Street West
Hamilton ON L8N 3Z5
Phone: 905 521-2100, Ext. 76295
Fax: 905 577-8468
Email: zadvorny@hhsc.ca

All interested and qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. Hamilton Regional Laboratory Medicine Program and McMaster University are committed to employment equity and welcome applications from all qualified persons. The positions will remain open until filled.

Academic Pediatric Pathologist
Hamilton Regional Laboratory Medicine Program
and McMaster University
Hamilton, Ontario

A position in Pediatric/Perinatal Anatomical Pathology is available in the Hamilton Regional Laboratory Medicine Program (HRLMP) and the Department of Pathology and Molecular Medicine at McMaster University. This full-time joint appointment in a large academic centre presents an excellent opportunity for an experienced academic pediatric pathologist or a recent graduate currently completing a pediatric pathology fellowship. The Hamilton Children’s Hospital is the second largest children's hospital in Ontario. The successful candidate will share service responsibilities with two other full-time pediatric pathologists as part of a larger regional anatomic pathology group with expertise in all pathology subspecialties, including neuropathology and forensic pathology. The Department of Pathology and Molecular Medicine is active in both undergraduate and postgraduate trainee teaching and members are expected to participate in research activities. The successful candidate will be presented for a faculty appointment, and academic rank will be determined by the qualifications of the applicant. The position is available as of January 1, 2010.

Applicants must be certified in Anatomical Pathology by the Royal College of Physicians and Surgeons of Canada or equivalent and must be eligible for registration with the College of Physicians and Surgeons of Ontario.

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Interested candidates are invited to submit a cover letter, curriculum vitae and the names and addresses of three referees by December 31, 2009 to:
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All interested and qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. Hamilton Regional Laboratory Medicine Program and McMaster University are committed to employment equity and welcome applications from all qualified persons. The position will remain open until filled.
The Department of Laboratory Medicine at St. Michael’s Hospital invites applications for a full time faculty position as an Anatomic Pathologist in the Division of Pathology. The successful candidate will receive an academic appointment in the Department of Laboratory Medicine and Pathobiology, University of Toronto, with the appropriate academic rank.

Applicants must have a M.D. or M.D./Ph.D. degree and be certified in Anatomic Pathology by the Royal College of Physicians and Surgeons of Canada, or equivalent. Requirements include formal training and experience in general surgical pathology, excellent diagnostic skills, and strong academic credentials. The position involves diagnostic service, teaching, and development of a collaborative research program in clinical, applied or basic research.

The Division of Pathology has 16 pathologists and is affiliated with 4 other divisions in the Department of Laboratory Medicine. A molecular biology laboratory is associated with anatomic pathology, as well as automated immunohistochemistry and electron microscopy services.

The University of Toronto is strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, Aboriginal persons, persons with disabilities, members of sexual minority groups and others who may contribute to the further diversification of ideas.

A letter of interest, and a list of references, should be sent with a C.V. before December 31, 2009, or until position is filled, to:

Dr. Serge Jothy, Chief, Department of Laboratory Medicine
St. Michael’s Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8
Tel: (416) 864 5972 Fax: (416) 864-5648
E-Mail: jothy@smh.toronto.on.ca

The Department of Laboratory Medicine at the Peterborough Regional Health Centre is seeking a pathologist trained in general pathology to fill a part-time position (0.4 FTE), vacant due to a recent retirement. The successful applicant will share responsibility with another general pathologist who also works part-time, and will be responsible for hematopathology sign-out and for supervision of the clinical pathology lab (core, microbiology, and transfusion medicine), as well as participation in the surgical pathology sign-out rotation.

Interested individuals may send a letter of application, including curriculum vitae, in confidence to:

Dr. Virginia M. Walley
Medical Director and Chief
Laboratory Medicine
Peterborough Regional Health Centre
1 Hospital Dr.
Peterborough, ON
K9J 7C6
or by email to: vwalley@prhc.on.ca

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**Toronto:** Princess Margaret Hospital/Ontario Cancer Institute
**Kingston:** Queen’s University
**Vancouver/Victoria:** BC Cancer Agency, Vancouver and Vancouver Island Centres
**Calgary:** Alberta Cancer Research Institute and Tom Baker’s Cancer Centre

Accepted fellows are funded by the program for 2 years to receive research training in the pathobiology and molecular pathology of human cancer. Trainees will be exposed to a comprehensive range of leading edge laboratory techniques and their applications to molecular pathology research. In addition to formal and self-directed learning, each fellow undertakes an in-depth research project that should lead to publication in high impact journals. Fellows may elect to combine or continue this training program in post-graduate studies that lead to a M.Sc. or Ph.D. degree.

This Training Program is designed for MD/MBChB pathologists who will have completed their residency or clinical fellowship and wish to develop additional research expertise for an academic career in molecular pathology.

For further information and application details please contact:

Dr. Ming-Sound Tsao
Tel. (416) 340-4737; e-mail: Ming.Tsao@uhn.on.ca

or

Margaret Juszczak
Tel. (416) 340-4800 ext. 5938; E-mail: Margaret.Juszczak@uhn.on.ca

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