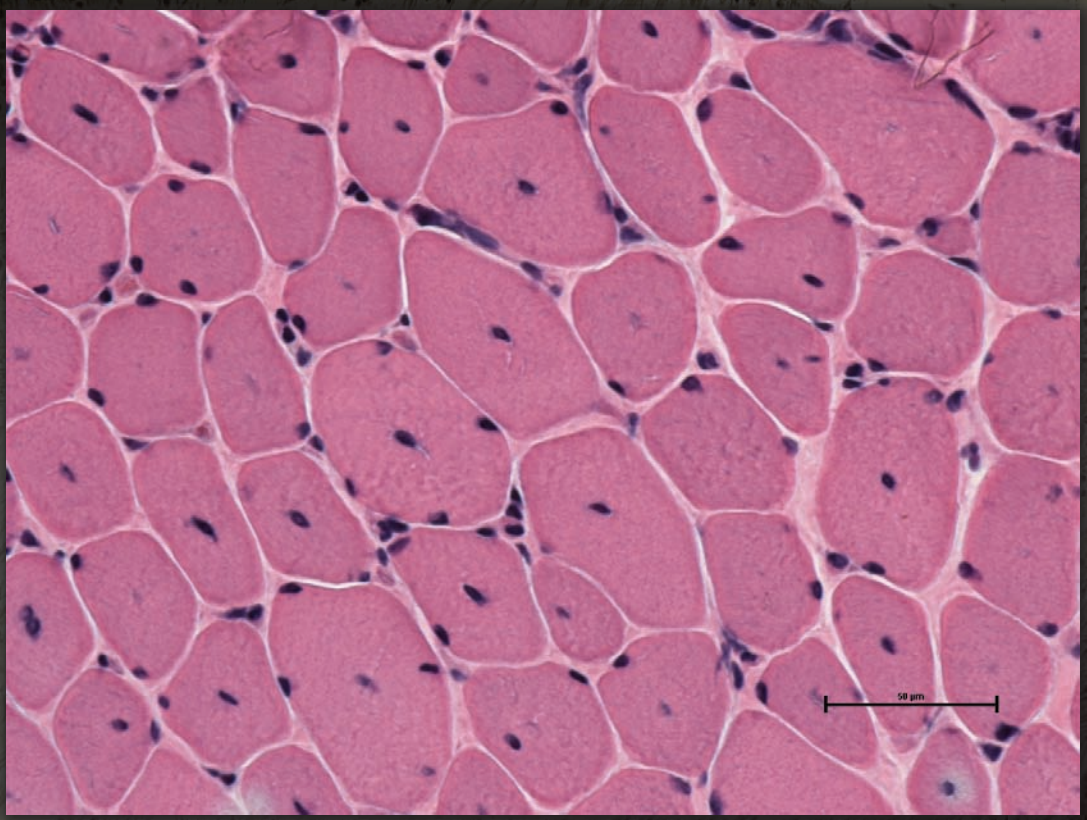
Volume 3, Issue 1 ▸ Spring 2011

Canadian Journal of Pathology

Official Publication of the Canadian Association of Pathologists



Canadian Laboratory Physician Supply: Falling Behind

Interpretation of Diagnostic Muscle Biopsies

Publications Agreement Number 40025049 ▸ ISSN 1918-915X

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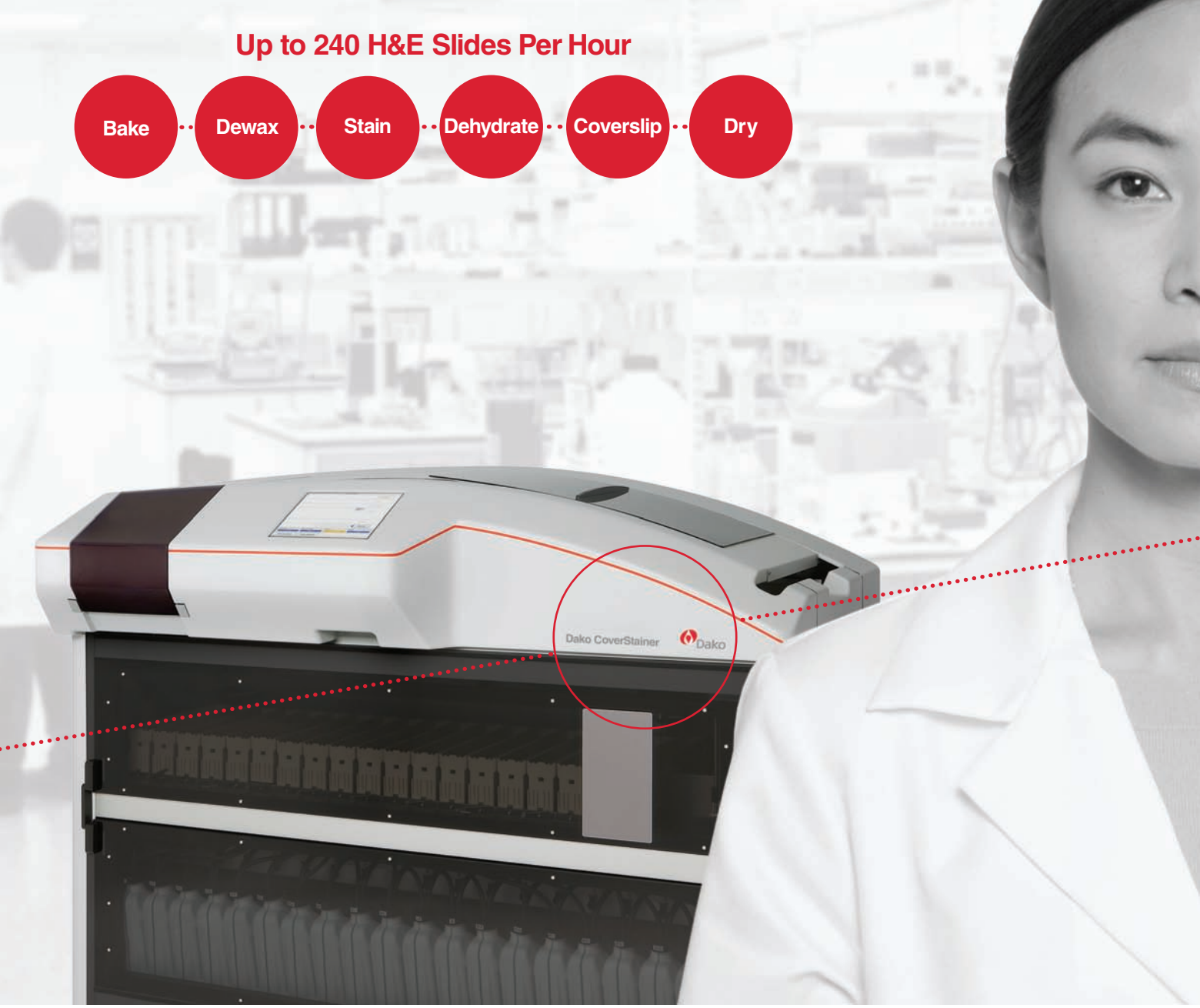

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Canadian Journal of Pathology
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Canadian Journal of Pathology • Volume 3, Issue 1, 2011

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Publications Agreement Number 40025049 • ISSN 1918-915X
Return undeliverable Canadian Addresses to:

AJP Andrew John Publishing Inc.

115 King Street West, Suite 220, Dundas, ON L9H 1V1

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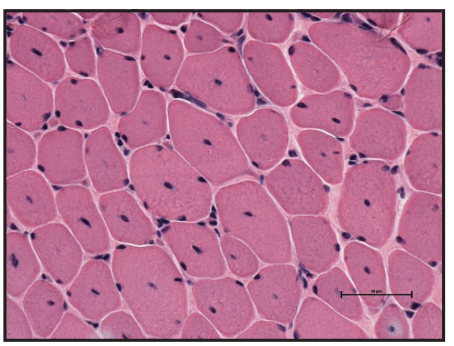

This image depicts skeletal muscle fibres showing widespread central nuclei in myotubular myopathy.

Two Years Later

With *Canadian Journal of Pathology (CJP)* now entering its third year, it is a good time to examine the journal's development over the 2 years since its inception. To assist in the evaluation, all members of the Canadian Association of Pathologists (CAP-ACP) were invited in November 2010 to participate in an online survey, although at that time only four scientific issues had been released. We received 113 responses out of 1,032 members surveyed (11%), and most questions were answered by over 94% of respondents.

It was encouraging to learn from the survey that 55% of respondents rated the overall content of the journal as very good or excellent, and only 3% rated it as poor. Similarly, 67% of respondents rated the overall appearance of the journal as very good or excellent, and only 3% regarded it as poor. Over 83% considered the journal to be relevant to their practice. Between 85 and 90% of respondents indicated that articles were well written and informative with images and illustrations of high quality.

Although this "snapshot" of readers' opinions was indeed gratifying, the request for lists of topics that should be covered in the journal provided evidence to support these opinions. Among the topics suggested, quality assurance, particularly in anatomical pathology, and how it might be achieved in smaller community hospitals, was clearly a major interest. Other suggestions focused on areas of professional practice, including workload, human resources, standardized reporting, and laboratory management in general, as well as the history of Canadian pathology. Articles on some of these topics have already appeared in the early issues of the journal and others have been accepted for publication.

There was general support for the continuation of regular invited reviews, dealing with both broad areas of systemic pathology and difficult or problem topics, as well as reviews of new technologies and updates in pathobiology written for a broad readership. This issue contains a masterful and comprehensive review on the interpretation of muscle biopsies, not perhaps a matter of daily concern to most, and the next will include a guide to the use of immunohistochemistry in dermatopathology that will be of practical value to all surgical pathologists.

The survey indicates that for many readers the journal is heading in the right direction, and perhaps the silent majority agree. Constructive criticisms are always more useful than vague plaudits, however, and there were some negative comments that made me, as editor-in-chief, pause to re-evaluate the goals of *CJP*. One anonymous respondent commented: "There is no need for a Canadian pathology journal. It has no impact, and I would rather send my contributions to well-established and read journals."

Clearly, it is good that Canadian pathologists, whose research is of sufficient calibre, should strive to have their work published in journals such as *Nature* or *The American Journal of Pathology*. For most Canadian pathologists, that is not an option; and valuable contributions to the understanding and practice of pathology are not confined to the pages of such prestigious journals. We can learn much from the practice of pathology and laboratory medicine in other countries, but ultimately we will have to solve our own particular problems. One of the major weaknesses of Canadian pathology and laboratory medicine has been its fragmentation within a provincially funded health care system. That this fragmentation has been to nobody's benefit is recognized by the recent decision to create a Canadian Pathology and Laboratory Medicine Leadership Council, which the president of CAP-ACP discusses in her letter on page 6. Whether or not this initiative is successful remains to be seen, but *CJP* offers us a way to share the developments and experiences in our fragmented system in a way that can benefit the whole country.

At this time, *CJP* is not indexed in PubMed and therefore has no impact factor. Whether it has a real impact depends on the usefulness of its contents to practising pathologists across Canada. The editorial board did not set out to create a Canadian journal of surgical pathology but, rather, to model our publication more on *Journal of Clinical Pathology*, with its discipline-wide scope. We recognize that it will take years, perhaps decades, to develop a significant impact factor for a new general specialty journal such as ours.

I would like to thank those readers who completed the survey and encourage all of you to consider submitting your studies to the journal. Your comments on published articles and matters of concern to Canadian pathologists, laboratory physicians, and scientists will always find space in our correspondence section.

J. Godfrey Heathcote
Editor-in-Chief

Deux ans plus tard

Alors que la *Revue canadienne de pathologie (RCP)* amorce sa troisième année d'existence, il semble opportun d'examiner son parcours depuis sa création. En prévision de cette évaluation, l'Association canadienne des pathologistes (CAP-ACP) a invité ses membres à répondre à un sondage en ligne en novembre dernier après la publication de quatre numéros scientifiques seulement. En tout et pour tout, 113 des 1 032 membres sollicités ont répondu au questionnaire (taux de réponse de 11 %), et 94 % des répondants ont répondu à la plupart des questions.

L'analyse des résultats révèle que 55 % des répondants estiment que le contenu de la revue est soit très bon, soit excellent, que seulement 3 % le jugent passable. De même, 67 % des répondants sont d'avis que l'apparence générale de la revue est soit très bonne, soit excellente, tandis que 3 % des répondants la trouvent médiocre. Pour plus de 83 % des répondants, la revue s'avère pertinente dans leur pratique. Enfin, de 85 % à 90 % des répondants affirment que les articles sont de bonne tenue et instructifs, qu'ils s'accompagnent d'images et d'illustrations de grande qualité.

Bien que cet « instantané » de l'opinion du lectorat soit gratifiant, la liste des sujets proposés en réponse à notre demande de sujets qui devraient faire parler d'eux dans la revue vient étayer ces propos. Le sujet de l'assurance de la qualité, particulièrement en anatomopathologie, et du mécanisme d'assurance de la qualité approprié dans le petit hôpital communautaire, est indéniablement un sujet d'intérêt majeur. La liste comprend en outre des sujets ayant trait à l'exercice de la profession, notamment la charge de travail, les ressources humaines, le compte rendu normalisé et la gestion du laboratoire en général, ainsi qu'à l'histoire de la pathologie au Canada. Des articles sur certains de ces sujets ont déjà paru dans les premiers numéros de la revue, d'autres sont prévus.

En général, les lecteurs souhaitent retrouver des articles de fond de collaborateurs invités, que ce soit sur des sujets de vaste portée relevant de la pathologie systémique, sur des sujets problématiques ou encore sur de nouvelles technologies ou sur les percées de la biopathologie d'intérêt général. Le présent numéro renferme un article de fond éminent et exhaustif sur l'interprétation de la biopsie musculaire, un sujet qui déborde peut-être du cadre de la pratique courante de la plupart d'entre nous, tandis que le prochain proposera des lignes directrices sur l'immunohistochimie en dermatopathologie qui se révéleront certes d'utilité pratique pour tous les pathologistes spécialisés en pathologie chirurgicale.

Les résultats du sondage indiquent que, pour beaucoup de lecteurs, la revue est sur le bon chemin, et peut-être que la majorité silencieuse en convient également. Néanmoins, la critique constructive demeure sans doute plus utile que les acclamations générales, et certaines observations défavorables m'ont porté à réfléchir, en tant que rédacteur en chef, sur les buts de la *RCP*. Un répondant a dit ceci dans l'anonymat : « Il n'y a pas lieu d'avoir une revue canadienne sur la pathologie. Ça n'a aucun impact, et j'aimerais mieux que mes articles paraissent dans des revues réputées qui font autorité. »

Il est clair que le pathologiste canadien dont les projets de recherche sont d'envergure a tout intérêt à voir ses travaux publier dans des revues telles *Nature* ou *The American Journal of Pathology*. Cependant, pour la plupart des pathologistes au pays, cela n'est pas possible, et les communications qui contribuent à l'avancement des connaissances sur la pathologie et de l'exercice de la profession ne sont pas réservées qu'à ces revues prestigieuses. Bien sûr, nous pouvons tirer des enseignements utiles sur la pathologie et la biologie médicale d'autres pays, mais, au bout du compte, nous aurons à régler nos problèmes particuliers. La compartimentation de l'exercice de cette branche de la médecine dans les réseaux de santé publics provinciaux en constitue l'une des grandes lacunes. La récente création du Conseil canadien de la pathologie et de la biologie médicale, sujet abordé par la présidente de l'Association à la page 6, illustre à quel point cette compartimentation est désavantageuse. Reste à savoir si cette initiative sera fructueuse, mais la *RCP* nous permet d'échanger entre nous sur les faits nouveaux et les expériences dans notre système compartimenté afin que tous au pays puissent en bénéficier.

Actuellement, étant donné que la *RCP* n'est pas indexée dans PubMed, nous ne connaissons pas son facteur d'impact, soit l'indicateur mesurant son influence. Son influence réelle dépend du caractère utile de son contenu pour les pathologistes en exercice au pays. Le comité de rédaction n'avait pas l'intention de diffuser une revue canadienne sur la pathologie chirurgicale, mais bien de publier une revue sur le modèle du *Journal of Clinical Pathology* qui s'intéresse à tous les champs de pratique de la discipline. Nous savons fort bien qu'il faudra des années, plusieurs dizaines d'années peut-être, avant qu'une nouvelle revue spécialisée d'ordre général comme la nôtre exerce un facteur d'impact important.

Je tiens à remercier les lecteurs qui ont répondu au sondage et je vous invite à faire publier vos études dans les pages de la revue. Sachez que la rubrique du courrier des lecteurs réservera toujours un bon accueil à vos observations sur les articles et sur les sujets d'intérêt pour les pathologistes, les médecins biologistes et les scientifiques canadiens.

J. Godfrey Heathcote
Rédacteur en chef

Message from the President

Dear CAP-ACP Members,

It is my pleasure to provide an update on the activities of the CAP-ACP since our very successful Annual Meeting in Montreal in July 2010. The executive met in Toronto in November and moved a number of projects forward. Some of these projects, as well as other activities of the CAP-ACP, are highlighted below.

CAP-ACP Office

The CAP-ACP Office with the executive are reviewing the bylaws and terms of reference for committees and working groups, as well as fine-tuning an organizational chart and job descriptions for positions in the organization.

Survey

We thank members for participating in a recent survey. A detailed report will be shared with members, but, overall, members appear satisfied with the work of the CAP-ACP. There was strong encouragement to develop online self-assessment programs (SAPs) in line with the new Royal College Maintenance of Certification (MOC) Program, which now awards three credits per hour for participation in SAPs. There will be a session on the new MOC Program at the upcoming Annual Meeting in Vancouver in June.

Guidelines

Work has begun to update guidelines, including those for retention of pathology material, led by Vina Alexopoulou, and telepathology, led by Bernard Têtu. Guidelines for quality assurance, including turnaround times, will be developed in the near future.

Continuing Professional Development

We successfully renewed our status as a Royal College Accredited Provider of Continuing Professional Development (CPD), and accreditation is being managed by a new Accreditation Subcommittee. In addition to accrediting our Annual Meeting and our Immunohistochemistry Meeting, we co-developed and accredited a series of distributed education sessions on the College of American Pathologists (CAP) cancer checklists with Cancer Care Ontario and the Canadian Partnership against Cancer (CPAC). A session on the TNM system is to be offered in April. The sessions can be accessed live or online after the event. We also co-developed and accredited an ongoing educational series on molecular pathology. We are working with CAP to offer a Canadian version of a course on breast pathology that is currently being offered in the United States. The course is composed of on-site group learning and online self-assessment modules, and these are being accredited for the Royal College MOC Program.

An immunohistochemistry course will be scheduled later in the year, and a molecular pathology course will precede the Annual Meeting in June. The CAP-ACP is endorsing a conference being organized by Emina Torlakovic in collaboration with the University Health Network titled Redefining the Crucial Role of the Pathologist in the Era of Personalized Medicine: The Development of a National Strategy.

The CPD Committee, under Joan Sweet, continues to expand the offerings of online CPD, and we urge members to contribute cases.

Website

The website is very active, providing regular updates on CAP-ACP activities. It also provides an online venue for discussion.

Canadian Journal of Pathology

Canadian Journal of Pathology is entering its third year. Founded under the leadership of past president Jagdish Butany, it is starting to flourish, featuring articles of high quality and interest. We urge members to contribute suitable papers. The *Journal* published the abstracts from the 2010 Annual Meeting online and will do so again for the upcoming Annual Meeting.

Annual Meeting

The Annual Meeting will be held from June 4 to 8 in Vancouver and will occur in partnership with the Canadian Society of Clinical Chemists. The Annual Meetings Committee, under Avrum Gotlieb, the Local Organizing Committee, under Diponkar Banerjee, and the CPD Committee, under Joan Sweet, are working hard to make this one of the most successful meetings ever.

Also mark your calendars for upcoming Annual Meetings

in Calgary, July 21–25, 2012, and in Quebec City, June 8–12, 2013, in partnership with the World Association of Societies of Pathology and Laboratory Medicine.

Andrew Herzenberg Award

At the Executive Meeting in Toronto in November, the memory of Dr. Andrew Herzenberg, who tragically passed away just before the Annual Meeting, was honoured by a gathering with some of his family members and friends, and a presentation of the Junior Scientist Award to his family. At the same event, we announced the founding by the executive of the Andrew Herzenberg Award for the best paper by a resident on nephropathology or transplant pathology at the Annual Meeting. Members will have an opportunity to contribute to the fund for the award at the time of membership renewal, or at any other time, through the CAP-ACP Office.

Resident Review Course

Under the leadership of Vina Alexopoulou, Jagdish Butany, and a board and faculty of CAP-ACP members, the first Resident Review Course will be offered in Hamilton from March 25 to 27 (see details on page 9). Registration numbers are high, and this event promises to be an ongoing and valuable service to our junior colleagues.

CAP-ACP Sections

The Canadian Society of Cytopathology and the sections of Haematological Pathology, Autopsy Pathology, Neuropathology, Advanced Diagnostics and Pathology Assistants, among others, continue work on a number of issues and a more detailed update of their activities will be provided at the time of the Annual Meeting.

Patient Safety and Quality Assurance

The Task Force on Guidelines on Investigation of Laboratory Medicine Irregularities, led by Diponkar Banerjee, developed Guidelines on Investigation of Laboratory Medicine Irregularities, and these are now posted on the website.

The National Standards Committee on Immunohistochemistry Testing, under Emina Torlakovic, produced class I and II checklists on immunohistochemistry, posted on the website, and expanded to become the National Standards Committee on High Complexity Laboratory Testing, which will also develop guidelines on molecular testing.

Anatomical Pathology

Pat Shaw, in collaboration with the Anatomical Pathology section chair, Anne O'Brien, formed a working group that will produce a statement on the pathologist as custodian of tissue.

Special Interest Groups

Joining five other special interest groups (SIGs), the Semen Analysis SIG was formed under the leadership of David Moore.

Collaboration with Other Organizations

Canadian Partnership against Cancer

In addition to the educational efforts mentioned above, we continue working with CPAC on many other fronts, including establishing Canadian cancer committees to provide Canadian input into the CAP cancer checklists and the national pathology synoptic reporting effort. The CAP-ACP was involved in the preparation for a CPAC press release earlier this year on the National Staging Initiative. CPAC continues to provide funding for a number of CAP-ACP activities, including CPD.

Royal College

The CAP-ACP is represented on the Royal College Specialty Committees for Anatomical Pathology by Vina Alexopoulou and General Pathology by Chris Naugler. Marciano Reis chairs both the CAP-ACP Section of Haematological Pathology and the Royal College Specialty Committee for Haematological Pathology. We urge members to communicate any comments or concerns they have about residency training issues to our representatives so that they can bring them to the attention of the Royal College.

The Royal College organized a Consensus Conference on Laboratory Medicine on November 15, 2010. The CAP-ACP was a member of the planning committee, and many CAP-ACP members were chairs, speakers, and participants in the conference. The press release that followed the conference

created much interest in the media, as well as from other laboratory medicine national specialty societies, and it was clear that the CAP-ACP is regarded by the media and the public as the spokesperson for laboratory medicine in Canada. There were articles in newspapers and online. The news release was published in the Royal College *Dialogue*, and a very good overview of the activities of the CAP-ACP was published in the December 15 issue of the *Medical Post*.
It was resolved at the conference to form a Canadian Leadership Council on Laboratory Medicine (CLCLM) and committees of the council to work on areas within laboratory medicine, including workload, quality assurance, and education.
The CAP-ACP is currently part of a small working group developing terms of reference for the proposed council. The executive developed a CAP-ACP position statement on the CLCLM and requested input on the document from the CAP-ACP Council. The CAP-ACP Council represents a broad spectrum of groups in Canadian laboratory medicine. The final document was forwarded to the working group developing terms of reference. The position statement includes the following principles:

1. Laboratory physicians should lead the proposed council.
2. There should be broad and equal representation of laboratory physicians, including from all laboratory physician national specialty societies and CAP-ACP sections, and geographic representation from provincial societies and academic pathology departments.
3. There should be participation from organizations that impact laboratory medicine such as the Royal College, Canadian Medical Association, and others yet to be decided.
4. There should be patient representation.
5. It is suggested that at least one of the sessions of the proposed council occur at the CAP-ACP Annual Meeting since many members of the proposed CLCLM would be members of the CAP-ACP Council.

International Liaison Committee of Presidents

The CAP-ACP is represented on the International Liaison Committee of Presidents of Pathology Organizations. It is reassuring to learn that most of the issues that Canadian pathologists struggle with are the same issues that our colleagues in other countries face. Membership of this committee is also an opportunity to learn from the experience of our international colleagues.
The CAP-ACP contributed an article on Canadian pathology in the *Bulletin of the Royal College of Pathology* in Britain.

Thank You

As always, thank you for the important contribution you make as CAP-ACP members to the Canadian community of pathologists and the Canadian public. Above all, thank you to Daniele Saintonge and Heather Wieland in the CAP-ACP Office, without whom none of the above would happen.
A very happy and healthy 2011 to all!

Laurette Geldenhuys
President

1st Annual Canadian Association of Pathologists' Association canadienne des pathologistes Residents Review Course

Friday, March 25 to Sunday, March 27, 2011
McMaster University - Hamilton, ON

The Canadian Association of Pathologists'/Association canadienne des pathologistes is pleased to announce and invite all Canadian trainees, US trainees, CAP-ACP resident members as well as non-members and pathologists to the 1st Canadian Association of Pathologists' Residents Review Course in Anatomical Pathology to be held in Hamilton, Ontario at McMaster University's Michael G. DeGroote School of Medicine (MDCL-3020).

Friday - March 25, 2011		
1300-1315	Welcome	Dr. Laurette Geldenhuys
1315-1340	The RCPSC AP Exam - Format and General Information	Dr. David Driman
1340-1400	The Oral Exam – How to Perform at Your Best	Dr. David Driman
1400-1500	Gastro Intestinal	Dr. Jeremy Parfitt
1500-1515	Health Break	
1515-1545	Quality Assurance in Anatomical Pathology	Dr. Julianne Klein
1545-1615	Lab Administration - What the Junior Pathologist Needs to Know	Dr. Jagdish Butany
1615-1645	Nervous System	Dr. Robert Macaulay
1645-1715	Cardiovascular Surgical and Autopsy Pathology – An Overview	Dr. Vidhya Nair
1715-1745	Pediatric Pathology Review	Dr. Jorge Arredondo
Saturday - March 26, 2011		
0730-0800	Continental Breakfast	
0800-0830	Diagnostic Immunohistochemistry	Dr. Emina Torlakovic
0830-0930	Head and Neck	Dr. Ilan Weinreb
0930-0945	Health Break	
0945-1000	Kidney Pathology – Medical	Dr. Vina Alexopoulou
1000-1045	Kidney, Ureter and Bladder – Surgical	Dr. Andrew Evans
1045-1145	Prostate and Testis	Dr. Andrew Evans
1145-1215	Skin Pathology	Dr. Martin Trotter
1215-1315	Lunch	
1315-1415	Pancreatic Pathology Review Liver Pathology: Understanding the Clinical Process	Dr. Jasim Radhi (pancreas) Dr. Oyedele Adeyi (liver)
1415-1445	Gross Pathology	Dr. Michele Weir
1445-1515	Breast Pathology Review	Dr. Penny Barnes
1515-1530	Health Break	
1530-1630	Pathology of the Female Genital Tract	Dr. Maire Duggan
1630-1700	Molecular Pathology for the Practicing Pathologist	Dr. Kenneth Craddock
1700-1730	Lung and Pleura	Dr. Jean-Claude Cutz
Sunday - March 27, 2011		
0730-0800	Continental Breakfast	
0800-0900	Forensic Pathology - What the Junior Pathologist Needs to Know	Dr. Matt Bowes
0900-1000	Cytology – Review of Basic Principles	Dr. Linda Kapusta
1000-1030	Health Break	
1030-1130	General Principles of Approach to Interpretation of Bone and Soft Tissue Pathology	Dr. Snezana Popovic
1130-1230	Overview of Benign and Malignant Haematological Disorders and Application of Ancillary Tests in Diagnosis and Prognosis	Dr. Monalisa Sur
1230-1330	Lunch	
1330-1430	Wrap-up and Self-Assessment	Dr Vina Alexopoulou and Dr. Jagdish Butany

Accreditation
The 1st Annual Canadian Association of Pathologists'/Association canadienne des pathologistes Residents Review Course is accredited by the Canadian Association of Pathologists. This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of The Royal College of Physicians and Surgeons of Canada.

FOR FULL COURSE DETAILS AND REGISTRATION PLEASE VISIT WWW.CAP-ACP.ORG

In Praise of the Part-Time Pathologist

Ann Hall, MD, FRCPC

The recent increases in pathologists' remuneration are a double-edged sword.[1] Many would argue that they represent a long overdue game of "catch-up" for a group of highly skilled and under-valued professionals facing a diminishing recruitment pool.[2] As a group that has little in the way of personal overhead commitment, this can be reflected in a degree of departmental staffing instability worthy of the installation of a revolving door. Many pathologists are paid under the global budget of the institution for which they provide services. This may come as a salary with benefits, contract, or fee-for-service arrangement with a hard cap. Regardless of the payment system, with the increased monetary value assigned, there is heightened scrutiny of workload. Since 2005, in the province of Ontario, many pathologists work under a Laboratory Medicine Funding Framework Agreement (LMFFA), which determines a uniform minimum level of compensation (UMLC) that increases each fiscal year. This has been a successful technique that has brought more uniform compensation to the profession. However, the ultimate goal is to link workload to compensation. Workload is the new currency in areas where there is levelling of the remuneration playing field. In conjunction with this greater value placed on pathologists' services, there has been an augmentation in case complexity and scrutiny and a push for standardization with rigorous quality assurance.[3] In general, workload seems to have increased, and pathologists now have empirical tools to measure this.[4,5]

When faced with a greater and greater workload, the difficulty lies in managing this volume. This is especially problematic in a small department, where there are fewer pathologists to carry the extra load. In general, the full-time pathologists absorb the extra workload, resulting in longer hours; this can contribute to burnout and longer turnaround times. This continues until an extra position is approved by the hospital administrators. The irony is that the busier one is with patient care, the more management issues – such as tracking workload, monitoring turnaround time, and engaging in quality assurance initiatives – take a back seat.

A way to alleviate this situation is to anticipate and plan when staffing a department. If a department is staffed with a core of full-time pathologists and a few part-time pathologists, managing the workload becomes dynamic. Flexible scheduling can accommodate slower periods, such as operating room shutdowns during the summer and peak holiday times. Likewise, increased staffing can be introduced during times of volume growth, such as the opening of a new endoscopy room or operating room.

When a department has a flexible pool of part-time pathologists, it can negate the need to ask, cap in hand, the administration for the funding to support a new full-time position. An incremental funding increase justified with workload data is more readily attainable. If a department commits to this data collection and can use it this way, administrators may even anticipate and budget for it over time. This funding increase can support extra days of coverage by part-timers, particularly when others are sick, on vacation, or on educational leave. This is an effective strategy to prevent stress and fatigue during times of increased caseload. Part-time staff offer other advantages to a department. They help promote a family-friendly atmosphere that can benefit recruitment and retention. They may also provide locums for other institutions, thus promoting networking, exposure to new ideas, and environmental scanning.

However, when one looks around the country, one sees many departments that are designed on the assumption that every pathologist must be full-time. I believe that part-time professionals are often viewed as less than dedicated to their profession. I have been fortunate to experience the opposite.

Ann Hall, MD, FRCPC, is a general pathologist, associate staff, at the Brant Community Healthcare System, Brantford General Hospital, in Brantford, Ontario; and a peer assessor for the College of Physicians and Surgeons of Ontario. She can be contacted at halan@bchsys.org. This article has been peer reviewed.

Competing interests: Dr. Hall works part-time at Brantford General Hospital. Until recently, she worked part-time at Cambridge Memorial Hospital and continues to provide locum coverage there.

For the last eight years of my professional career, I have been proudly working part-time in a small community hospital laboratory. We currently have six pathologists for four full-time positions. I have ranged from providing 0.3 to 0.7 full-time equivalents during this period, depending on the needs of the department. My level of professional enthusiasm is higher than when I was full-time. Working part-time forces me to scrutinize every report I issue to ensure clarity as I may not be at the hospital if a clinician questions my wording. My part-time colleagues and I have facilitated surge capacity and departmental growth.

I believe that greater consideration should be given to hiring part-time pathologists when planning departmental staffing needs. Before embarking on this approach, it might be wise to consider discussion with pathologists who have successfully integrated part-time colleagues. There is no need to reinvent the wheel. Accept that every department has different workflow priorities and that flexibility is required.

References

1. Ontario Ministry of Finance. Public sector salary disclosure 2010. Toronto (ON): The Ministry, 2010; http://www.fin.gov.on.ca/en/publications/salarydisclosure/2010/. Accessed February 2, 2011.
2. Physician Working Group, Provincial Advisory Group, Ontario Regional Laboratory Services Planning Program. A Discussion paper on laboratory physician human resources issues in Ontario. Why is the shortage of laboratory physicians/pathologists different from other physician shortages? Toronto, ON: The Group, 2002; https://www.oma.org/Member/Community/Sections/LAB/Documents/2002LabPhysicianShortages.pdf.
3. de Baca ME, Madden JF, Kennedy M. Electronic pathology reporting digitizing the College of American Pathologists cancer checklists. Arch Pathol Lab Med 2010;134:663–4.
4. Maung R. What is the best indicator to determine anatomic pathology workload? Canadian experience. Am J Clin Pathol 2005;123:45–55.
5. Maung R. Canadian Association of Pathologists guidelines for measurement of workload. Canadian Journal of Pathology 2010;2(1):8–19.

ORIGINAL ARTICLE

Canadian Laboratory Physician Supply: Falling Behind

Aaron F. Pollett, MD, Ginette Lajoie, MD, Terence J. Colgan, MD

ABSTRACT

Purpose: High-quality pathology and laboratory medicine require a sufficient supply of laboratory physicians. This study sought to identify trends in the supply of laboratory physicians over the past decade.

Methods: Physician supply data were retrieved from the "*Supply, Distribution and Migration of Canadian Physicians*" of the Canadian Institute for Health Information for the years 1998 and 2008. Three measures of laboratory physician and/or pathologist supply were defined and then calculated: (1) population-to-laboratory physician and population-to-pathologist ratios; (2) clinical physician-to-laboratory physician ratio; and (3) comparison of population-to-pathologist and population-to-radiation oncologist ratios.

Results: All three of the chosen demographic parameters indicate that the supply of laboratory physicians and/or pathologists has diminished in the past decade, relative to population, clinical physician, and radiation oncologist numbers. Supply trends varied by province and parameter, but the supply of laboratory physicians for clinical physicians fell in most provinces.

Conclusions: Current trends in the supply of laboratory physicians give rise to concerns. If these trends continue, an adverse impact on Canadian health care can be expected.

RÉSUMÉ

But : L'offre de services de qualité dans les domaines de la pathologie et de la biologie médicale est une question notamment d'effectifs médicaux suffisants dans ces disciplines. La présente étude a pour objectif de cerner les tendances qui marquent les effectifs de pathologistes et de médecins biologistes dans les dix dernières années.

Méthode : L'information sur la main-d'œuvre médicale des années 1998 et 2008 provient de la publication *Nombre, répartition et migration des médecins canadiens* de l'Institut canadien d'information sur la santé. Nous avons calculé la proportion des effectifs de médecins biologistes et de pathologistes par rapport à la population (ratio médecins biologistes-population et ratio pathologistes-population) et le rapport entre les médecins cliniciens et les médecins biologistes; enfin, nous comparons entre eux les ratios pathologistes-population et radio-oncologues-population.

Aaron F. Pollett, MD, and Terence J. Colgan, MD, are members of the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, University of Toronto, in Toronto, Ontario. Ginette Lajoie, MD, is a member of the Department of Laboratory Medicine, Brampton Civic Hospital, William Osler Health System, in Brampton, Ontario. Correspondence may be directed to Terence J. Colgan at tcolgan@mtsinai.on.ca.

This article has been peer reviewed.

Competing interests: The authors are practising pathologists in Ontario.

Résultats : Les trois paramètres démographiques choisis indiquent que les effectifs de médecins biologistes et de pathologistes ont diminué dans la dernière décennie, par rapport à la population, aux médecins cliniciens et aux radio-oncologues. Les tendances de l'offre varient selon la province et le paramètre; à noter, cependant, que l'effectif de médecins biologistes par rapport à l'effectif de médecins cliniciens a reculé dans la plupart des provinces.
Conclusion : Les tendances qui caractérisent l'effectif de médecins biologistes à l'heure actuelle sont préoccupantes. Si elles se maintenaient, la situation pourrait entraîner des répercussions de taille sur le système de santé au pays.

High-quality clinical and pathology laboratories are essential to Canadian health care. Indeed, in the past decade there has been renewed interest in improving the quality of laboratory testing and consultation.[1–3] Medical leadership and consultation by laboratory physicians are key components in establishing and maintaining these high-quality laboratories. There are no Canadian studies on trends in the supply of laboratory physicians even though it is generally recognized that an increased supply of health care professionals is required to meet the demographic challenge of Canada's aging population. The purpose of this Canada-wide study was to determine whether there has been any demonstrable trend in laboratory physician and pathologist supply in the past decade.

Materials and Methods

This study used data exclusively from the *Supply, Distribution, and Migration of Canadian Physicians* reports of the Canadian Institute for Health Information (CIHI).[4] The CIHI is a not-for-profit independent organization created by the federal, provincial, and territorial governments and is dedicated to forging a common approach to Canadian health information. Physician data were derived primarily from Scott's Medical Database[5] and then verified or supplemented through cross-reference with data from the Royal College of Physicians and Surgeons of Canada, the College of Family Physicians, and the Collège des médecins du Québec. Active physicians include all those in clinical practice or those with a valid address. Residents and military, non-licensed, and semi-retired physicians are excluded from the database.

Although the CIHI database recognizes six laboratory specialties, two specialist groupings were defined for the purposes of this study. The first group consisted of laboratory physicians working in all six laboratory specialties (i.e., anatomical pathologists, general pathologists, neuropathologists, hematopathologists, medical microbiologists, and medical biochemists). The second group consisted of pathologists only, a subset of laboratory physicians that encompasses anatomical and general pathologists and neuro- and hematopathologists. All non-laboratory physicians were designated "clinical physicians"; these included family practitioners, clinical specialists of internal medicine, and surgical specialists.

Many microbiologists are also qualified in infectious disease and consequently could be listed in either the clinical medicine or the laboratory medicine category. Any change in the listing of this group between the years 1998 and 2008 could potentially impact trends. An assessment of the CIHI database suggested that this had not happened since microbiologists made up a similar proportion of laboratory physicians in 1998 (16.3%) and 2008 (16.8%).

The following three parameters were defined and then used to measure the supply of laboratory physicians and pathologists:

1. **Population-to-laboratory physician or pathologist ratio.** This parameter is an established measure of laboratory physician supply and is based upon the assumption that the need for laboratory services and consultations is directly correlated with population size.
2. **Clinical physicians-to-laboratory physician ratio.** Laboratory testing and pathology consultations are performed at the request of clinical specialists and family practitioners. In both institutional and community laboratory settings, each laboratory physician or pathologist supports a number of clinical specialists and family practitioners in their daily practice. In this parameter, the number of clinical physicians (i.e., both clinical specialists and family practitioners) per laboratory physician was calculated.
3. **Comparison of population-to-pathologist and**

population-to-radiation oncologist ratios. Cancer diagnosis and monitoring of cancer management is a major component of pathology practice. Owing to the aging of Canada's population, the increase in the incidence of cancer exceeds that of the population. Consequently there is a growing need for the provision of oncologic diagnosis and treatment. The only clinical oncology specialty that can be identified in the CIHI database is radiation oncology. This specialty was used as a measure of the changes in oncologist supply to meet the growing demand for cancer management.

Provincial and Canadian data from the CIHI database were extracted for 1998 and 2008. Subsequently the three parameters were calculated for each of the 2 years. The difference between 1998 and 2008 was calculated, followed by the proportional (percentage) change from the base year, 1998. The year 1998 was used as the study's reference point, but this was an arbitrary choice and does not imply that 1998 represents an ideal or optimal state for supply. A ratio that increased between 1998 and 2008 signified a decreased supply. Conversely, a ratio that decreased between 1998 and 2008 signified an increased supply.

Results

The supply of Canadian physicians as reflected in the population-to-physician ratio is shown in Table 1. In brief, the overall supply of physicians increased by 4.8% between 1998 and 2008. This increased supply was entirely attributable to family practice and to clinical medical specialties since both surgical and laboratory specialties registered a decreased supply (i.e., an increase in their population-to-physician ratios). Of the nine surgical specialties, the following six experienced an increased population-to-physician ratio (i.e., a decreased supply): general surgery, cardiothoracic surgery, ophthalmology, otolaryngology, plastic surgery, and urology. The remaining three (neurosurgery, obstetrics, and orthopedics) experienced decreased population-to-physician ratios.

Changes in laboratory physician supply varied across Canada. Five provinces (Alberta, Manitoba, New Brunswick, Prince Edward Island, and Nova Scotia) did show a stable or decreased population to-laboratory physician ratio, but the three largest provinces by population (Ontario, Quebec, and British Columbia), along with Newfoundland and Saskatchewan, all experienced a decline in laboratory physician supply, ranging from 1.2 to 31.6% from 1998 to 2008 (Table 2).

Table 1. Supply of Canadian Physicians: Population-to-Practitioner Ratio by Specialty Groups, 1998 versus 2008

	1998	2008	Change in Supply (%)
Family practitioners	1,060	994	↑ 6.2
Clinical medical specialists	1,635	1,529	↑ 6.5
Surgical specialists	3,912	4,068	↓ 4.0
Laboratory physicians	21,311	21,686	↓ 1.8
Pathologists	27,612	27,991	↓ 1.4
All physicians	538	512	↑ 4.8

Table 2. Provinces Showing Decrease in the Supply of Laboratory Physicians by Population-to-Laboratory Physician Ratio, 1998 versus 2008

	1998	2008	Change in Supply (%)
Saskatchewan	19,943	26,251	↓ 31.6
British Columbia	18,498	19,644	↓ 6.2
Ontario	23,744	24,784	↓ 4.4
Quebec	18,276	18,753	↓ 2.6
Newfoundland	16,769	16,967	↓ 1.2
Canada	**21,311**	**21,686**	**↓ 1.8**

Table 3. Provinces Showing Decrease in the Supply of Pathologists by Population-to-Pathologist Ratio, 1998 versus 2008

	1998	2008	Change in Supply (%)
Saskatchewan	23,653	31,024	↓31.2
British Columbia	22,322	23,636	↓5.9
Ontario	27,587	28,418	↓3.0
Quebec	33,844	37,237	↓10.0
Canada	**27,612**	**27,991**	**↓1.4**

Similar trends were evident with respect to the supply of pathologists during the same period (Table 3). Only a minor increase in the population-to-pathologist ratio was noted for Canada overall (1.4%). This decreased pathologist supply was entirely attributable to four provinces whereas the six other provinces had stable or increased pathologist numbers. The four provinces experiencing declines in pathologist supply were Saskatchewan, British Columbia, Ontario, and Quebec; declines ranged from 3.0 to 31.2%.

The second parameter, the ratio of clinical physicians to laboratory physicians, is shown in Table 4. In 1998 there were 38.5 clinical physicians for each Canadian laboratory physician. By 2008, this ratio had increased to 41.4, an increase of 7.5%. In seven provinces, the ratio increased by 0.5 to 43.0% (Table 5).

Table 4. Clinical and Laboratory Physicians in Canada, 1998 versus 2008

	1998	2008	
Clinical physicians	54,722	63,865	
Laboratory physicians	1,420	1,545	
Ratio of clinical to laboratory physicians	38.5	41.4	(↑7.5%)

Table 5. Provinces Showing Increased Ratio of Clinical Physicians to Laboratory Physicians, 1998 versus 2008

	1998	2008	% Increase
Saskatchewan	29.0	41.5	43.0
Newfoundland	27.9	36.0	29.0
British Columbia	34.7	39.3	13.3
Alberta	38.7	43.7	12.9
Quebec	37.6	40.1	6.6
Ontario	41.5	43.0	3.9
New Brunswick	40.1	40.3	0.5
Canada	**38.5**	**41.4**	**7.5**

Table 6. Supply of Canadian Pathologists and Laboratory Physicians Compared with Radiation Oncologists: Population-to-Practitioner Ratios, 1998 versus 2008

	1998	2008	Change in Supply (%)
Radiation oncologists	99,547	87,709	↑ 11.9
Pathologists	27,612	27,991	↓ 1.4
All laboratory physicians	21,311	21,686	↓ 1.8

The third parameter, the ratio of pathologists to radiation oncologists, is shown in Table 6. From 1998 to 2008, the ratio of the Canadian population to radiation oncologists decreased by 11.9%, indicating a significant improvement in supply. During the same time period, the supply of both laboratory physicians and pathologists decreased slightly, as indicated by increases of less than 2% in the population-to-practitioner ratio.

Discussion

From 1998 to 2008, the Canadian population grew by 10.7%, presenting a challenge to Canada's physician supply. Nevertheless, the overall supply of physicians met this challenge, leading to an improved population-to-physician ratio of almost 5% (from 538 to 512). In contrast, there has been a slight decrease in both the laboratory physician (1.8%) and pathologist (1.4%) supply. The overall supply of surgical specialists also dropped (see Table 1). This study cannot identify the reason or reasons for the increased ratio of population to surgical specialists or whether such a decreased supply could be appropriate with shifting technologies and emerging subspecialties in clinical internal medicine.

Not surprisingly, there is variability among the provinces with respect to any change in laboratory physician supply (see Table 2). With the exception of Newfoundland, the same provinces that experienced a drop in laboratory physician supply also showed a drop in pathologist supply (see Table 3).

In addition to overall population growth, health care faces

increased demand for clinical services by an aging population. The second parameter, the ratio of clinical physicians to laboratory physicians, examines whether the growth in clinical physicians is matched by a similar growth in laboratory physicians since laboratory testing and consultations underpin clinical practice and diagnosis. The data clearly demonstrate that each laboratory physician is "supporting" more clinical physician practitioners in Canada overall (see Table 4) and in seven of Canada's 10 provinces, including the four most populous provinces (see Table 5). Notably, even Alberta, which had maintained a stable or slightly improved laboratory physician supply, showed a 12.9% increase in the ratio of clinical physicians to laboratory physicians during the same period. To maintain the 1998 ratio of clinical physicians to laboratory physicians (38.5) would have required an increase of 114 laboratory physicians across Canada in 2008. This is approximately the total number of laboratory physicians practising in the three provinces of Nova Scotia, Newfoundland, and New Brunswick in 2008.

From 1998 to 2008, the supply of radiation oncologists increased by almost 12% (see Table 6) while that of both pathologists and laboratory physicians registered a slight decrease. Undoubtedly, one of the drivers of the increased supply of radiation oncologists is the federal wait-times strategy, which rewards provinces that meet benchmarks for cancer treatment wait times. These benchmarks do not include a wait time for pathological diagnosis, thus providing no incentive for bolstering pathology capacity.[6]

What is the appropriate laboratory physician supply for the Canadian health care system? The data from this study cannot address this central question. Laboratory automation, which has greatly improved productivity in the technical components of laboratory testing, does not provide opportunities for improved efficiencies in the medical practice of laboratory medicine and pathology. Both the regionalization of laboratory services (which occurred throughout most Canadian provinces either prior to or during the period of this study) and the movement toward subspecialty practice in all areas of laboratory medicine may have provided opportunities for improving professional efficiency. On the other hand, laboratory physicians and pathologists must meet the demands of a growing list of new or expanding activities, including infectious epidemic response and planning, increasing test menus, forensic pathology, case complexity, quality management, novel screening programs, and "personalized medicine" with requisite molecular pathology and "pharmacopathology." These growing demands likely outweigh the efficiencies that may have been realized through laboratory restructuring and subspecialization.

Why have clinical physicians been able to meet the Canadian demographic challenge whereas laboratory physicians have not? In most provinces, the vast majority of clinical services are performed on a fee-for-service basis, thus providing a link between demand and remuneration. In contrast to these clinical physicians, most Canadian laboratory physicians are remunerated largely or entirely through salary or contract with the hospital, regional system, or province. Within this arrangement, laboratory, regional, and/or governmental administrators are often reluctant to recognize the need for more laboratory physician positions or to enhance the attractiveness of current unfilled positions. As more physicians are encouraged to adopt salaried or contractual arrangements similar to those for laboratory physicians, the supply trends of laboratory physicians should become of greater interest to the medical profession as a whole. Although workload systems for some areas of laboratory medicine have been devised, acceptance by both laboratory physicians and administrators in light of the funding implications has often been difficult.[7–9]

In conclusion, all three of the selected demographic parameters indicate that the supply of laboratory physicians and/or pathologists relative to population, clinical physicians, or radiation oncologists has diminished in the past decade. Some provinces have been more affected than others. The impact of a diminishing supply of Canadian laboratory physicians, if any, needs to be identified. At a minimum, it will likely have an effect on the ability to institute new (or maintain existing) quality management programs.

References

1. Lett D. Canada lags in standardized protocols for medical labs [news]. CMAJ 2008;179:125–6.
2. Message from the CEO, July 2008 – report on Royal College Activities. The Royal College of Physicians and Surgeons of Canada, 2008;

http://rcpsc.medical.org/about/CEO/Message_CEO_July_2008_e.pdf. Accessed June 15, 2010.
3. Chorneyko K, Butany J. Canada's pathology [Editorial]. CMAJ 2008;178:1523–4.
4. Supply, distribution, and migration of Canadian physicians. Canadian Institute for Health Information, 2008; http://secure.cihi.ca/cihiweb/dispPage.jsp ?cw_ page=PG_2510_E&cw_topic=2510&cw_rel=AR_14_E. Accessed June 24, 2010.
5. Scott's Medical Database; http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page= hhrdata_smdb_e. Accessed September 30, 2010.
6. Colgan TJ. Has Canada's wait list strategy made pathologists the "Cinderella" of oncologists? Can J Pathol 2009;1:33–4.
7. Horne GJ, Barber DF, Bruecks AK, et al. Workload measurement in subspecialty dermatopathology. J Clin Pathol 2009;62:385–6.
8. Maung RT. What is the best indicator to determine anatomic pathology workload? Canadian experience. Am J Clin Pathol 2005;123:45–55.
9. Carr RA, Sanders DS, Stores OP, et al. The Warwick system of prospective workload allocation in cellular pathology – an aid to subspecialisation: a comparison with the Royal College of Pathologists' system. J Clin Pathol 2006; 59:835–9.

ORIGINAL ARTICLE

The Development and Delivery of a Pathology Objective Structured Clinical Examination for Postgraduate Pathology Trainees

Marla Nayer, PhD, William Chapman, MD, FRCPC

ABSTRACT

Previously, a slide-based oral examination was used by Ontario pathology residency program directors to select international medical graduate pathologists for residency positions in Ontario. The primary focus of this examination was the CanMEDS Medical Expert role. The directors decided to expand the scope of the examination to address the range of competencies and skills required by pathologists and to develop an examination with acceptable reliability and validity and that was easy to administer. This article describes the evolution from a traditional slide-based oral test to an objective structured clinical examination (OSCE). The new examination addresses the Medical Expert, Collaborator, Communicator, Professional, and Manager roles. The OSCE format and results obtained were validated with a group of Canadian residents. This format is appropriate for assessing pathology residents in Canadian residency programs.

RÉSUMÉ

Par le passé, les directeurs de programme de résidence en pathologie de l'Ontario ont eu coutume de sélectionner les médecins diplômés à l'étranger candidats à un poste de résidence en leur faisant subir une épreuve orale prenant la forme d'un diaporama. L'épreuve était centrée principalement sur le rôle d'expert médical selon le cadre de référence CanMEDS. Puis, les directeurs ont convenu d'élargir la portée de l'épreuve à la gamme des compétences et des aptitudes que doit posséder le pathologiste et de concevoir un examen de fiabilité et de validité raisonnables, facile à administrer. L'article retrace l'évolution de l'épreuve orale classique qui s'est transformée en un examen clinique objectif structuré (ECOS). Ce nouvel examen porte sur les rôles d'expert médical, de collaborateur, de communicateur, de professionnel et de gestionnaire. La forme et les résultats de l'ECOS ont été validés auprès d'un groupe de médecins résidents canadiens. L'examen est tout à fait propre à évaluer les médecins résidents en pathologie au pays.

Marla Nayer, PhD, is a member of the Centre for the Evaluation of Health Professionals Educated Abroad, in Toronto, Ontario. William Chapman, MD, FRCPC, is a member of the Department of Laboratory Medicine and Pathobiology, University of Toronto, in Toronto, Ontario. Correspondence may be directed to m.nayer@cehpea.ca.
This article has been peer reviewed.
Competing interests: None declared

In 2002, the Canadian Task Force on Licensure of International Medical Graduates was established with a mandate to aid in the integration of international medical graduates (IMGs) into the Canadian workforce of physicians. The Task Force presented its recommendations in 2003. The first recommendation was to "increase the capacity to assess and prepare IMGs for licensure."[1] International Medical Graduates Ontario (IMGO) was established by the Ministry of Health and Long-Term Care in 2004 in response to this recommendation, and assessments were developed for family medicine and for 11 specialties, including pathology. In 2007, IMGO was closed, and the Centre for the Evaluation of Health Professionals Educated Abroad (CEHPEA) was established. CEHPEA's mandate is twofold: (1) to assess IMGs in order to determine their eligibility for placement in postgraduate year 1 (PGY1), postgraduate year 2 (PGY2), or practice-ready assessment (PRA) positions, and (2) to provide an orientation program for IMGs who have been accepted into residency positions. Pathology was a highly sought-after specialty during the early years of IMGO and CEHPEA. In the first 3 years, more than 30 candidates applied for pathology (either anatomical or general) assessment (Table 1) although numbers declined during the past two application cycles. The format used for assessing the suitability of IMG pathologists for residency positions in the first few years of IMGO and CEHPEA was a slide-based oral examination that primarily tested the CanMEDS Medical Expert competency. This format was time consuming, given the size of the group, and did not address other competencies. The Ontario Pathology Residency Program directors expressed a desire to improve the reliability and validity of the examination, to expand the scope beyond the Medical Expert competency, and to simplify the administrative process.

Table 1. Numbers of Applicants for Assessment in Pathology

Application Cycle	Number of Applicants
2004–2005	33
2005–2006	30
2006–2007	38
2007–2008	9
2008–2009	10

This article describes the evolution of the advanced placement assessment process for applicants to general or anatomical pathology, from a traditional oral examination to an objective structured clinical examination (OSCE) format that specifically focuses on the broader range of competencies and skills required by pathologists.

The Pathology Assessment Process

Pathology applicants have been assessed for advanced placement at the PGY2 or PRA levels since the 2004–2005 application cycle. These two entry points are based on an agreement between the Royal College of Physicians and Surgeons of Canada (RCPSC) and the IMG assessment programs used in Ontario since the 2004–2005 cycle. This agreement allows candidates who have been assessed as ready to enter a residency at the PGY2 level to be granted an exemption by the RCPSC from completing PGY1. Similarly, those who have been assessed as ready to enter a PRA position are granted an exemption from completing the entire residency. To be eligible for the PGY2 assessment, candidates must have completed at least 1 year of postgraduate education in pathology. (In most cases, this would have been in the candidate's home country.) To be eligible for consideration at the PRA level, candidates must have been in independent pathology practice within the previous 5 years.

The assessment includes both a written and a clinical examination. Program directors from the various faculties of medicine in Ontario oversee the examination processes. These individuals provide expertise in specialty-specific content as well as in various contextual factors (environmental, educational, and political) related to the assessment and selection of applicants for advanced entry positions. The purpose of the written examination is to assess the candidate's basic and applied knowledge of the specialty. During the initial discussions, the oversight group for pathology was consulted on the selection of an appropriate written examination. The examination selected was the Resident-In-Training Examination administered by the American Society for Clinical Pathology. The oversight group confirmed that this examination was appropriate for the assessment of candidates' basic and applied knowledge of pathology.

The purpose of the clinical examination is to evaluate specialty-specific medical knowledge, skills, attitudes, and behaviour. For pathology, the skills evaluated may include aspects of medical expert/clinical problem solving but should also include aspects of other CanMEDS competencies, such as Communicator, Collaborator, Health Advocate, Manager, and Professional. The format originally chosen for this examination was a slide review and an oral examination based on the slide review. This format assesses the Medical Expert and clinical decision-making competencies and (to some extent) the Communicator competency but fails to address the other competencies necessary for the practice of pathology.

Development of the Pathology OSCE

From 2004 to 2006, the clinical examination for pathology consisted of a review of two or three slides. Candidates were given half an hour to review the slides, after which they underwent an oral examination with questions about the slides and about clinical scenarios. Two examiners were present for this oral examination, and scoring was based on a specified answer key for the particular questions asked.

The advantages of this format were that (1) all of the candidates were presented with the same slides and clinical scenarios, (2) two examiners evaluated each candidate, which is an improvement over having only a single assessor, and (3) the format was similar to that of the oral examination for pathology prescribed by the RCPSC. The disadvantages were the following:

- Only two examiners evaluated each candidate, compared with an OSCE, which could provide multiple assessor ratings.
- Candidates were evaluated by different examiners.
- There was no specific standard-setting process.
- Scores tended to rank candidates in a particular order rather than indicating a readiness for residency.
- The format primarily addressed only the CanMEDS Medical Expert and (to some extent) Communicator competencies.

At the start of the 2007–2008 application cycle, five pathologists (two of whom were program directors) attended a workshop on examination development at which they discussed the content of the examination and the possibility of creating an OSCE, a format that had not previously been used for pathology examinations.

Developed in the 1970s, the OSCE is generally thought of as a method of assessment that includes interactions with standardized patients. However, the original premise was that the OSCE is merely an examination format and that different types of stations can be included. For example, while the majority of OSCEs use standardized patients, other stations may consist of written components (including the writing of admission orders) and reviews of radiography or laboratory test results.

The examination that was developed from this workshop in 2007 was a nine-station OSCE. The nine stations included the following:

- Four stations with a slide review and written responses (including report preparation)
- One oral station with a slide review
- Two oral stations that assessed both the Medical Expert and Communicator competencies
- Two stations with "standardized colleagues" to assess the Medical Expert, Communicator, Collaborator, and Professional competencies

The "standardized colleagues" in the last two stations were individuals who portrayed colleagues of the physician candidates (for example, laboratory employees or other physicians with whom the candidate had to interact). Standardized colleagues were played either by physician examiners or by nonmedical individuals who were trained for the specific role of medical colleague.

The time spent at each station was 15 minutes. Eight examiners participated: five were examiners at stations, two marked the written responses, and the lead program director served as the chief examiner.

The scoring format depended on the station. The candidates' responses in the four stations with slide reviews and written responses were scored by two examiners working independently. The two examiners used scoring guides with explicit criteria for awarding marks to the written responses. The examiners then provided an overall

opinion of each candidate's performance at that station by using the following rating scale: unsatisfactory; comparable to PGY1, PGY2, or PGY2+; or PRA. Descriptions of each level of training were provided to the examiners (Table 2). These descriptions were generic in nature as they were used across multiple specialties assessed at CEHPEA. On the morning of the examination, the chief examiner led a discussion on how these descriptions related specifically to pathology residents.

Candidates' performances at the oral stations and at one of the two stations for interaction with a standardized colleague were scored by one examiner, again with explicit scoring criteria. The examiner also provided an overall opinion of each candidate's performance at that station, using the rating scale in Table 2. At the second standardized-colleague station, one examiner rated the candidate on six domains (Table 3) and also provided an overall opinion, using the global ratings listed earlier. Each rating level (PGY1, PGY2, etc.) was assigned a point value as shown in Table 2.

The total number of marks obtained at each station was converted into a percentage score to provide a total score for that station. The total scores for the nine stations were averaged to derive the final test score for each candidate. Following the examination, the examiners for each station were asked to identify the scores that would designate a candidate at a PGY2 level and a PRA level. The chief examiner conducted this exercise for all of the stations because he was familiar with the entire examination. For the written-response stations, the two examiners who had marked each station conducted this exercise; these two scores were then averaged to produce a passing score for each station. Finally, the passing scores for all stations were combined to produce a passing score for the overall examination. The final passing scores for this examination were 55% for the PGY2 level and 85% for the PRA level.

The advantages of this OSCE approach were that (1) all of the candidates were presented with the same slides and clinical scenarios, (2) there were eight examiners (instead of two) involved per candidate, and (3) a specific standard was described. Data for inter-rater reliability were collected for the written-response stations by having two examiners mark

Table 2. Descriptions of Performance Levels

Level	Description	Point Value
Unsatisfactory	Below PGY1	1
PGY1	Could function as a resident. Demonstrates skill in judgment, synthesis, caring, effectiveness. In addition to what a clerk can do, able to generate a treatment plan that will become increasingly comprehensive and detailed. Is efficient and organized in history taking and physical examination. Skilled and selective in treatment planning, understanding of limits, and assuredness. Balanced demonstration of technical and humanistic skills. Able to deal with common conditions with typical presentation.	2
PGY2	Could function as a resident. Demonstrates skill in judgment, synthesis, flexibility, caring, effectiveness. Able to individualize the treatment plan for the patient, taking into account contraindications, patient preferences, cost, etc. Is increasingly efficient and organized in history taking. Basic competence in treatment planning. Understanding of limits and abilities as a professional. Increasingly acting as if this is their patient (i.e., not just the staff doctor's patient). Increasingly able to deal with common and uncommon conditions with typical presentations. Demonstrates openness, confidence, and assuredness as a communicator. Balanced demonstration of competence as a medical expert and professional.	3
PGY2+	Senior resident; above PGY2 level but not yet PRA.	4
Practice ready	Could practice without supervision. Could function as an independent practitioner. Professionally sophisticated; able to integrate adequate knowledge, interpersonal skills, assumption of responsibility. Able to deal with complexity and indeterminacy. At an exemplary level, enough competence to act as a resource to other health care professionals would be implied.	5

PGY = postgraduate year; PRA = practice-ready assessment.

Table 3. Domain Descriptions for Interactive Station, 2007–2008

Colleague Encounter	Notes
Verbal communication skills	Demonstrates fluency in verbal communications (e.g., grammar, vocabulary, tone, volume).
Nonverbal communication skills	Demonstrates responsiveness. Demonstrates appropriate nonverbal communications (e.g., eye contact, gesture, posture, use of silence).
Response to colleague's feelings, needs, values	Shows respect, establishes trust; attends to patient's needs of comfort, modesty, confidentiality, information.
Organization	Maintains a coherent and succinct approach.
Management of error resolution	Explains rationale for test/treatment/approach, obtains patient consent, educates/counsels regarding management; performs appropriate management; considers risks, benefit.
Post-Encounter Probe	**Notes**
Understanding of responsibilities	It is the responsibility of a pathologist to report errors found in colleagues' reports and deal with them in a collegial manner.

each candidate's score sheet. Overall, the examination provided greater coverage of the CanMEDS competencies. The disadvantages of this approach were that (1) it was operationally challenging, (2) the examiners lacked familiarity with the format for this specialty, and (3) there were different scoring structures for written-response stations and interactive stations.

During the 2007–2008 cycle, five candidates were assessed with this OSCE. Analysis was conducted with the Statistical Package for the Social Sciences (SPSS) version 16. The interstation alpha coefficient was 0.57. (Alpha is a measure of a test's internal consistency; it signifies the extent to which the items –in this case, OSCE stations – measure the same construct, namely, expertise in pathology. The higher the correlations between the scores on each station, the higher the value of alpha.) Given the small sample size, this reliability must be interpreted with caution. All five IMG candidates passed at the PGY2 level, with scores ranging from 57% to 72%. Despite the challenges, the examiners (three of whom were program directors) were pleased with the information obtained from the examination and from the interactions with the candidates and recommended that the development of this format should continue.

For the 2008–2009 application cycle, the pathologists who attended the workshop on station development created a more comprehensive blueprint. Eight competencies or roles and five subdomains were identified for assessment at all future examinations (Table 4). The station developers then created stations that would address these competencies, roles, and subdomains. The comprehensive blueprint

Table 4. Pathology OSCE Blueprint

	Subdomains of Pathology				
Competencies or Roles	**Surgical/Histology/ Ancillary Studies**	**Clinical Pathology**	**Gross Pathology**	**Cytology**	**Forensic Autopsy**
Error					
Communication					
Manager/safety					
Written/synoptic report					
Diagnostic accuracy					
Quality assurance					
Ethics/professionalism					
Medical expert					

Table 5. Domain Descriptions for Interactive Stations, 2008–2009

Domain Description	Notes
Data collection	Collects appropriate information prior to answering questions.
Verbal communication skills	Demonstrates fluency in verbal communications (e.g., grammar, vocabulary, tone, volume).
Working diagnosis	Obtains correct diagnosis.
Differential diagnoses	Identifies most likely causes of the disorder.
Investigation	Selects appropriate diagnostic studies/treatments; considers risks, benefits, and costs.
Organization	Uses an approach that is coherent and succinct.
Case management	Explains rationale for test/treatment/approach at appropriate level for colleagues; educates/counsels regarding management.
Content knowledge	Demonstrates knowledge of topic content appropriately.

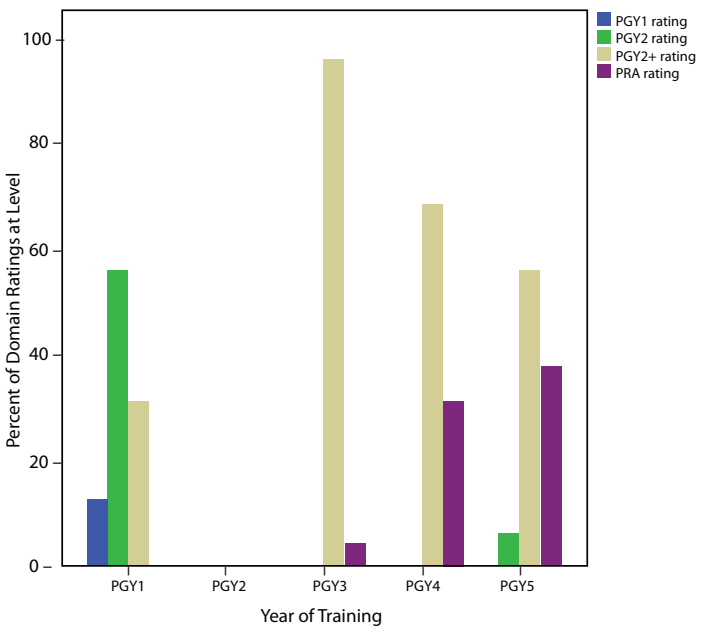

Figure 1. Higher-level residents receive higher-level ratings. (PGY = postgraduate year; PRA = practice-ready assessment)

resulted in a 12-station OSCE consisting of two stations with written assessment, six stations with slides or images with oral questions, and four stations with standardized colleagues. The interactive stations with standardized colleagues required communication with clinicians (surgeons and family physicians). Topics included addressing medical error (colleague error), educating a colleague, and assessing the Manager competency (laboratory safety issues).

Once again, scoring schemes were clearly articulated for all written questions (e.g., two points for question 1, five points for question 2); however, standardized ratings (from unsatisfactory to PRA) were used for all stations regardless of whether the format was written, oral, or interactive. Eight domains for assessment were standardized for all stations (Table 5). The written stations retained the specific numerical scoring for the responses but added these eight domain ratings plus an overall rating based on the five-point scale ranging from unsatisfactory to PRA. Only domains relevant to the station were scored; for example, verbal communication skills were not evaluated at the written-response stations. The total scores for a station were calculated as the mode of scores on all domains at that station. The total test score was calculated as the mode of the 12 station scores on the five-point scale. The feedback provided to candidates included ratings for each separate domain. These were the mode of all scores for that domain across all 12 stations (Appendix A).

The administration of this examination also included a validation study wherein 11 Canadian medical graduates (CMGs) intermingled with the nine IMGs. The CMGs were from PGY1, PGY3, PGY4, and PGY5. There were no PGY2 candidates owing to the scheduling of this examination close to the administration of Medical Council of Canada Qualifying Examination Part II.

Based on 20 candidates (9 IMGs and 11 CMGs), the intraclass coefficient for the 12-station OSCE was 0.82. The intraclass correlation signifies the extent to which the 12 examiners agree in their ratings of the candidates across the 12 stations. The higher the value of the intraclass correlation, the greater the agreement among examiners. All nine IMGs received passing scores at the PGY2 level. Eighty-eight ratings were generated among the 11 CMGs, one in each of

the eight competency domains for each candidate. The only group that received PGY1 domain ratings were the PGY1 residents (Figure 1). All but one of the PGY2 domain ratings was given to the PGY1 residents. One PGY5 CMG received one domain rating of PGY2 in the management of a case. Although a few PGY2+ ratings were given to PGY1 residents, almost all ratings given to PGY3 residents were at the PGY2+ level. As residents progressed in their training, examiner ratings increased. Although 95% of the PGY3 resident ratings were at the PGY2+ level, 37.5% of the ratings for residents in PGY5 were at the PRA level. This pattern of increasing levels of ratings with increasing years of education demonstrates that the OSCE was able to discriminate between lower- and upper-level residents.

Discussion

Traditional oral examinations can assess a component of the competencies expected of a pathology resident. Residents have pointed out that some areas of importance in residency, such as laboratory management, are inadequately covered.[2] There is a need to enhance education in working with others, and the CanMEDS framework is useful in guiding this process.[3] Broadening the clinical examinations to include standardized assessments of additional CanMEDS competencies may also ensure that education for residents in these areas will be increased.

It is possible to develop an OSCE for pathology residents that includes multiple CanMEDS competencies such as Medical Expert, Collaborator, Communicator, Professional, and Manager. Station development in the past 2 years has covered all but two objectives of the blueprint. A future workshop on station development will focus on the two remaining areas, ensuring that all examinations can meet the blueprint requirements. The program directors and examiners were positive about the assessment of additional competencies and recommended that this examination format continue for future application cycles.

Acknowledgement

The validation study discussed formed a part of the Quality Assurance Program at CEHPEA.

References

1. Canadian Task Force on Licensure of International Medical Graduates. Report of the Canadian Task Force on Licensure of International Medical Graduates, 2004.
2. Chen ZW, Morgen EK. Anatomical pathology training in Canada: perspectives from junior residents. Can J Pathol 2009;1:39–40.
3. Butany J. Pathology in Canada: today and tomorrow. Can J Pathol 2009;1:11–3.

Appendix A. Sample Candidate Rating Calculation

Sample Station Rating for Candidate 1

Colleague Encounter	Rating*
Data collection	PGY2
Verbal communication skills	PGY2
Working diagnosis	PGY1
Differential diagnoses	PGY2
Investigation	PGY2+
Organization	PGY2+
Case management	PGY2
Content knowledge	PGY2

PGY = postgraduate year.
*Candidate station rating = mode of all ratings at the station = PGY2 for this station.

Sample Examination Rating* for Candidate 1

Station	Station Rating
1	PGY1
2	PGY2
3	PGY2
4	PGY2+
5	PGY2
6	PRA
7	PGY2
8	PGY2+
9	PGY2
10	PGY2
11	PGY2
12	PGY2+

PGY = postgraduate year; PRA = practice-ready assessment.
*Candidate examination rating = mode of all station ratings = PGY2. Similarly, domain ratings were calculated as the mode of all ratings for that domain across all stations.

Malignant Mixed Germ Cell Tumour in a 13-Year-Old Boy with Familial Testotoxicosis

Susanne M. Chan, MD, Jose A. Gomez-Lemus, MD, FRCPC

ABSTRACT

Familial testotoxicosis is a rare condition with only one reported case of associated malignancy, a seminoma. We report the first case of familial testotoxicosis associated with a malignant mixed germ cell tumour.

RÉSUMÉ

La testotoxicose familiale est une affection rare; seul un cas rapporté lui associe un néoplasme malin, un séminome. Nous examinons ici le premier cas de testotoxicose familiale associée à une tumeur maligne des cellules germinales mixtes.

Case Report

A 13-year-old boy with longstanding familial testotoxicosis developed precocious puberty with accelerated growth and advanced skeletal age. A hypoechoic lesion measuring 1.6 × 1.3 × 1.0 cm was discovered in the right testis on ultrasonograms, and laboratory investigations revealed slightly elevated alpha-fetoprotein (AFP; 5.4 µg/L) and beta-human chorionic gonadotropin (hCG; 10 IU/L) levels. Testosterone levels (26.6 nmol/L) were markedly elevated, but levels of luteinizing hormone (LH; <0.1 IU/L) and follicle-stimulating hormone (FSH; <0.3 IU/L) were low. The patient underwent radical orchiectomy. A tan-white multinodular mass was evident on gross examination of the surgical specimen (Figure 1). The final pathological diagnosis was malignant mixed germ cell tumour consisting of embryonal carcinoma (60%), mature teratoma (35%), and yolk sac tumour (5%) (Figure 2). In the background testicular parenchyma, there was intratubular germ cell neoplasia unclassified (IGCNU), extensive Leydig cell hyperplasia, testicular microlithiasis, and evidence of spermatogenesis (Figure 3).

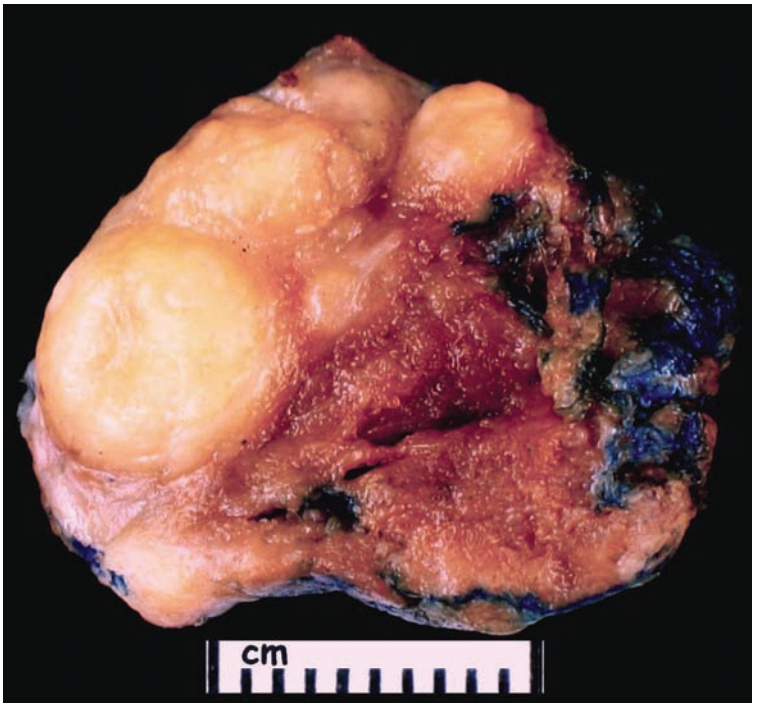

Figure 1. Gross photograph of multinodular testicular mass.

Susanne M. Chan, MD, and Jose A. Gomez-Lemus, MD, FRCPC, are members of the Department of Pathology, University of Western Ontario and London Health Sciences Centre, in London, Ontario. Correspondence may be directed to Jose A. Gomez-Lemus at Jose.GomezLemus@lhsc.on.ca.

This article has been peer reviewed.
Competing interests: None declared.

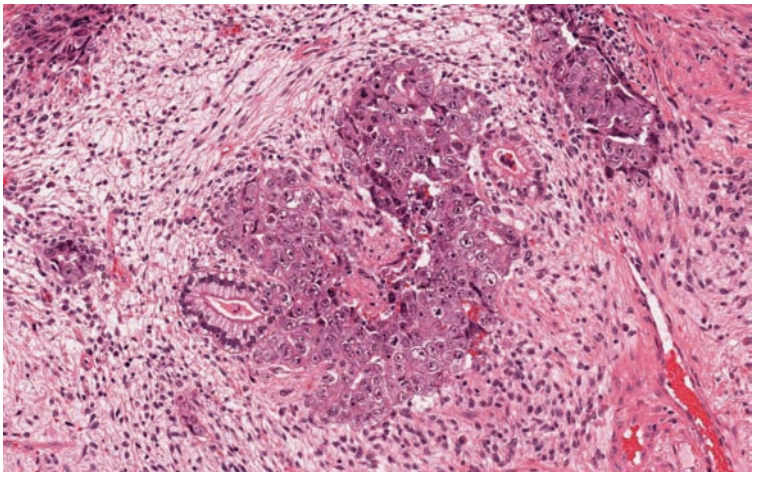

Figure 2. Embryonal carcinoma and teratoma within the mixed germ cell tumour. (Hematoxylin and eosin)

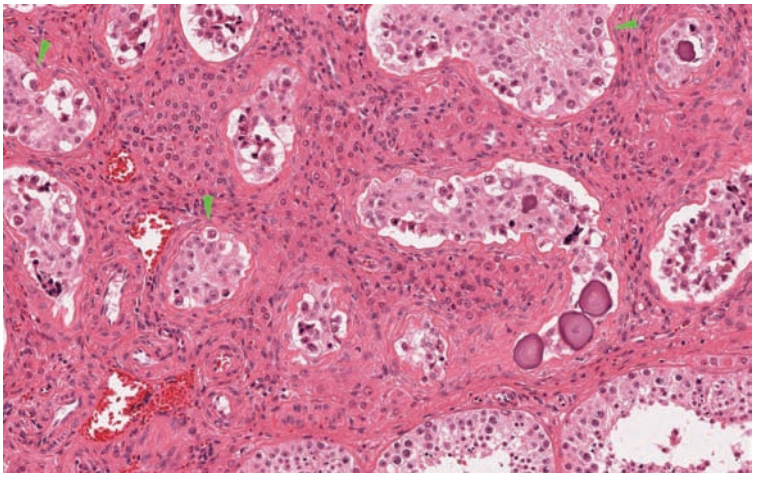

Figure 3. Background testicular parenchyma with intratubular germ cell neoplasia unclassified *(green arrowheads)*, extensive interstitial Leydig cell hyperplasia, spermatogenesis, and microlithiasis. (Hematoxylin and eosin)

Discussion

In familial testotoxicosis, an autosomal-dominant mutation in the LH receptor gene leads to early and constitutive activation of the receptors, resulting in elevated testosterone levels and precocious puberty.[1] The most common mutation in the United States is the $Asp^{578}Gly$ mutation, and occasional sporadic mutations do occur.[1] Although testosterone is elevated, LH and FSH levels remain at prepubertal levels, making testotoxicosis a form of gonadotropin-independent precocious puberty. Testotoxicosis is also sex limited in that it affects only males since females require both FSH- and LH-receptor stimulation for gonadal activation.[2] Clinically, males present with precocious puberty starting as early as age 1–3 years, with premature testicular enlargement, penile growth, development of secondary sexual characteristics, and accelerated skeletal development.[2,3] Early treatment in the form of anti-androgens and aromatase inhibitors may help delay or slow down the onset of puberty.[2]

Histologically, testicular Leydig cell hyperplasia, premature spermatogenesis, Sertoli cells with complex cytoplasmic differentiation, and Charcot-Böttcher crystals have been described in testotoxicosis.[3] Hyperplastic Leydig cell nodules and adenomas are also not uncommon.[4] However, only a single case of associated malignancy, a seminoma in a 37-year-old patient, has been previously reported.[5]

Our report is the first to describe a malignant mixed germ cell tumour associated with testotoxicosis. In our case, the patient had a background of ICGNU and microlithiasis, both of which are predisposed to testicular germ cell malignancies. Given that the average presenting age of malignant mixed germ cell neoplasms is 30 years,[6] the development of malignancy in this patient at age 13 may have been accelerated by early and sustained exposure to testosterone resulting from his underlying testotoxicosis.

References

1. Kremer H, Martens JW, van Reen M, et al. A limited repertoire of mutations of the luteinizing hormone (LH) receptor gene in familial and sporadic patients with male LH-independent precocious puberty. J Clin Endocrinol Metab 1999;84:1136–40.
2. Wu S, Leschek EW, Rennert OM, et al. Luteinizing hormone receptor mutations in disorders of sexual development and cancer. Pediatr Pathol Mol Med 2000;19:21–40.
3. Gondos B, Egli CA, Rosenthal SM, et al. Testicular changes in gonadotropin-independent familial male sexual precocity. Familial testotoxicosis. Arch Pathol Lab Med 1985;109:990–5.
4. Leschek EW, Chan WY, Diamond DA, et al. Nodular Leydig cell hyperplasia in a boy with familial male-limited precocious puberty. J Pediatr 2001; 38:949–51.
5. Martin MM, Wu SM, Martin AL, et al. Testicular seminoma in a patient with a constitutively activating mutation of the luteinizing hormone/chorionic gonadotropin receptor. Eur J Endocrinol 1998;139:101–6.
6. Adham WK, Raval BK, Uzquiano MC, et al. Best cases from the AFIP: bilateral testicular tumors: seminoma and mixed germ cell tumor. Radiographics 2005;25:835–9.

Mathematical Modelling of Lymph Node Grossing Techniques

Etienne Mahe, BSc, MD

ABSTRACT

The optimal histopathological handling of sentinel lymph nodes remains the subject of debate. There is surprisingly little evidence in support of the manner in which sentinel lymph nodes are grossed. Some authors recommend that a lymph node be sectioned parallel to the long axis of the node, while others recommend that the short axis be used. In either case, the manner in which a sentinel lymph node is grossed determines the cut surface area exposed for histological examination and, in turn, the amount of area examinable for the presence of metastases. In this article, mathematical models of each of these approaches are presented and compared from the perspective of optimization of cut surface area. Computer modelling and simulations are also performed in order to assess how variously sized lymph nodes should be optimally grossed and to assess how frequently an optimal approach improves theoretical tumour focus detection. The results favour the use of the long-axis approach.

RÉSUMÉ

Le débat fait toujours rage à propos de la préparation histopathologique optimale du ganglion sentinelle. Étonnamment, peu de données probantes déterminent le mode de préparation de ce ganglion. Des auteurs recommandent de le trancher en parallèle à son axe long, tandis que d'autres privilégient la coupe perpendiculaire à cet axe. Quoi qu'il en soit, l'angle de coupe détermine la surface exposée qui fera l'objet de l'examen histologique et, de ce fait, la taille de la zone examinée pour détecter la présence de métastases. L'article présente des modèles mathématiques des deux méthodes et les compare sur le plan de l'optimisation de la surface de la coupe sectionnée. La modélisation et les simulations informatiques permettent d'évaluer la préparation optimale de ganglions sentinelles de différentes tailles et de déterminer à quelle fréquence la méthode optimale améliore la détection théorique de cellules tumorales. Les résultats penchent pour la coupe parallèle à l'axe long.

Etienne Mahe is a member of the Department of Pathology and Molecular Medicine at McMaster University Medical Centre, in Hamilton, Ontario. Correspondence may be directed to etienne.mahe@medportal.ca.
This article has been peer reviewed.
Competing interests: None declared

The microscopic examination of lymph nodes is often an exercise in detection of tumour metastases. As outlined in the TNM staging system, lymph node metastasis, as part of the overall staging, is an indicator of tumour burden and outcome.[1] The effort devoted to the detection of small tumour foci has increased because the standard of care in many instances now requires sensitivity to isolated tumour cells.[2] Although the prognostic utility of a positive diagnosis of isolated tumour cells in a lymph node generally, and a sentinel lymph node specifically, remains debatable,[3–5] a recent meta-analysis has noted that the identification of low-volume tumour metastasis (i.e., isolated tumour cells or micrometastases) in a sentinel lymph node in breast cancer cases is associated with non-sentinel lymph node disease in 10–15% of cases. It is logical, therefore, from both a patient care and completeness perspective, that the identification of *any* metastases, whether in the form of isolated tumour cells, micrometastases, or macroscopic foci, should be the ultimate goal of the pathological examination of a sentinel lymph node. As the literature indicates, however, maximizing the probability that this goal is achieved, and in the greatest number of instances, is both heuristically difficult and open to debate on the basis of merit.[3–7]

As Weaver aptly notes in his review, a pathologist can never be absolutely confident that a lymph node is negative for disease, especially if he or she equates the presence of isolated tumour cells with "positive" for metastasis.[4] It follows that a certain level of error must be accepted as unavoidable, with the understanding that steps be taken to mitigate this error whenever possible. It is this mitigation of error that has sparked much research into the optimal histopathological evaluation of a sentinel lymph node. As long ago as 1948, it was recognized that a combination of deeper sectioning and retrospective review of slides could reduce the false-negative rate of lymph node evaluation.[8] More recently, immunohistochemistry has become important in detecting otherwise "occult" lymph node metastases. Weaver et al. noted that a combination of deeper sectioning and immunohistochemistry could improve the sensitivity of lymph node evaluation, with 75% of false-negative sentinel lymph nodes in their series containing isolated tumour metastases.[5] As much as deeper sections and immunohistochemical stains have been shown to reduce false-negative rates, the literature looking at the effect of the specific grossing techniques employed on the detection of nodal metastases is sparse.

Some sources have recommended that a lymph node be grossed by means of serial sections parallel to the long axis of the node; such a technique should maximize the histological visualization of the lymphatic channels serving the node and minimize the number of necessary tissue blocks.[3–9] Although intuitively logical, these arguments are incomplete. First, although serial sections through the long axis of a node may capture a number of lymphatic channels in a single section, there is insufficient evidence to say that multiple sections cut perpendicular to the long axis (and submitted in the same cassette moreover) would not do the same job as effectively. Furthermore, although the natural desire to reduce the total number of tissue blocks submitted for histological analysis is beneficial from a resource management perspective, the orientation of grossing (i.e., whether cuts are made parallel or perpendicular to the long axis) does not necessarily dictate the number of blocks since multiple smaller slices submitted when cutting perpendicular to the long axis may be placed in the same cassette. Moreover, a single slice taken parallel to the long axis may be so large as to necessitate multiple blocks. Finally, the localization and identification of lymphatic channels does not equate to the localization and identification of a tumour deposit since the very biology of a lymph node sees it acting as a sieve through which a tumour cell may trace out a path before taking root and forming a tumour focus. This latter point is exemplified by the seemingly random scattering of nevus cells that may periodically be observed in lymph nodes.

Still other authors have recommended that a sentinel lymph node be grossed by means of sections cut parallel to the short axis. In his recent review, Shidham noted that sentinel lymph nodes in cases of melanoma need to be grossed parallel to the short axis in order to maximize the delineable circumference on histological sections.[10] It is stated that, since melanoma tends to form subcapsular tumour foci, an extensive examination of the nodal circumference is warranted, and Shidham provides a mathematical derivation in support of his technique. Unfortunately, both of these arguments can be easily refuted. First, the argument

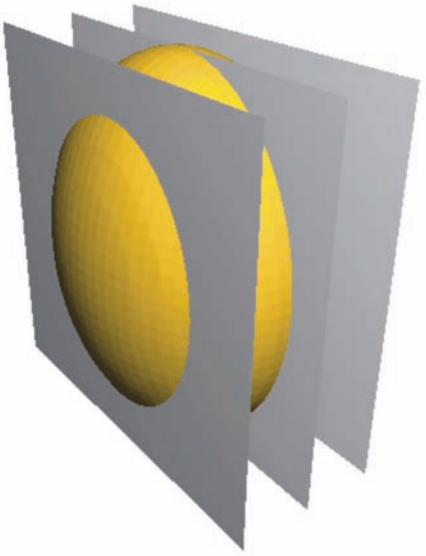

Figure 1. The long axis approach; sections taken parallel to the long axis.

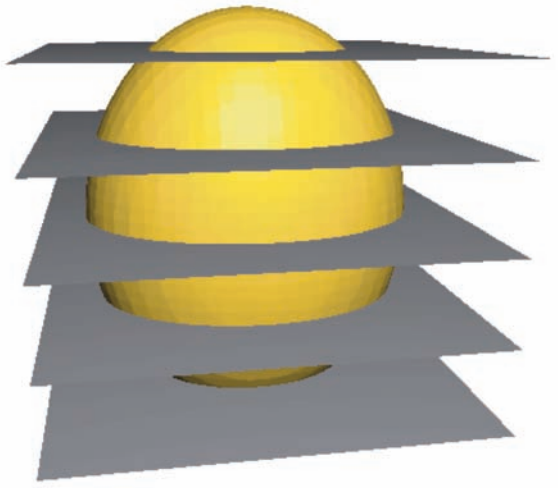

Figure 2. The short axis approach; sections taken parallel to the short axis.

that visualization of the nodal circumference should take precedence is faulted by the reality that tumour foci are not linear but, rather, three dimensional; maximizing the visibility of a uni-dimensional aspect of a tumour is therefore illogical when histological slides present tumour foci in two dimensions. Secondly, the mathematical derivations presented in his article are incomplete, and the summative effect of the circumference of multiple sections is not adequately accounted for. It would seem, therefore, that greater evidence in support of either of the grossing techniques described above is needed.

Since a lymph node cannot be examined in its entirety, it seems logical to try to maximize the cut surface area of the lymph node upon grossing to maximize the area that may be visible on a slide (and on subsequent deeper sections if needed). Thus, it may be surmised that the optimal detection of lymph node metastases may be improved if the grossing technique maximizes the cut surface area of a lymph node. From first principles there are three general methods in which a lymph node may be sectioned: with slices parallel to the long, short or intermediate axis. The intermediate axis approach is generally not chosen since, very simply, each slice taken in this manner will undercut the maximal surface area and will fail to produce the maximal number of slices. With respect to the other two methods, one (the "long axis" approach; Figure 1) will maximize the surface area of a given slice while sacrificing the total number of slices; the other (the "short axis" approach; Figure 2) will do the opposite. These two techniques are the extremes that are compared in this article. In either case, based on the College of American Pathologists' guidelines, sectioning begins with a central cut followed by further cuts moving outwards from the centre, with each tissue section taken at a thickness of 2 mm.[3,4,9]

Methods

A lymph node can be modelled mathematically by the ellipsoid centred at the Cartesian origin with semi-axes *a, b,* and *c* according to the following:

$$\frac{x^2}{a^2} + \frac{y^2}{b^2} + \frac{z^2}{c^2} = 1,$$
$$0 < a \leq b < c$$

This translates to a lymph node with long, short, and intermediate axis lengths, respectively, 2c, 2a, and 2b. This model need not take into account the perfect sphere since in this case the node would be grossed identically from any perspective. Other shapes such as the oval or the kidney-bean shape are not rigorously subsumed within this model since their equations are more complicated and cannot be easily described in Cartesian coordinates. In real life, however, the oval or bean-shaped lymph nodes can be approximated as ellipsoids since they usually have some amount of surrounding fat; in these cases the long, short, and intermediate axes can be measured and the shape approximated as an ellipsoid.

When sectioning the lymph node parallel to the short axis, surfaces with traces parallel to the x,y-plane are obtained; likewise, when sectioning the lymph node perpendicular to the long axis, surfaces parallel to the y,z-plane are obtained (see Appendix 1 at http://cap-acp.org/).

For each section in the short axis approach, the area of the trace ellipse is given by equation (6) of Appendix 1; the converse long axis approach is given by equation (7). When the cut surface areas exposed upon sectioning the entire node are summed, the following are obtained from equations (9) and (10):

Total Cut Surface Area, Short Axis Approach =

$$2\pi ab\left(\left\langle\frac{c}{2}\right\rangle+1-\frac{4}{6c^2}\left(\left\langle\frac{c}{2}\right\rangle\left(\left\langle\frac{c}{2}\right\rangle+1\right)\left(2\left\langle\frac{c}{2}\right\rangle+1\right)\right)\right)$$

Total Cut Surface Area, Long Axis Approach =

$$2\pi bc\left(\left\langle\frac{a}{2}\right\rangle+1-\frac{4}{6a^2}\left(\left\langle\frac{a}{2}\right\rangle\left(\left\langle\frac{a}{2}\right\rangle+1\right)\left(2\left\langle\frac{a}{2}\right\rangle+1\right)\right)\right)$$

(The angled brackets here refer to the floor function; see Appendix 1 at http://cap-acp.org/ for details.)

By comparing the values of the two equations for an individual node, the theoretical optimal surface area for each grossing technique can be determined. The specific technique producing the larger theoretical surface area should be chosen to maximize the optimal cut surface area available for histological evaluation.

To further analyze the optimal surface areas for each technique for nodes of various sizes, a computer analysis was performed to assess the optimal cut surface area of a hypothetical lymph node using either of the grossing techniques. In most laboratories, grossing is performed with a metric precision of 1 mm (i.e., the smallest gradations of grossing room rulers can be assumed to be 1 mm). Furthermore, most histopathology tissue cassettes can contain a maximal linear length of approximately 4 cm. Thus, using a range of axis lengths from 1 mm to 40 mm in increments of 1 mm, a reasonable approximation of possible lymph node sizes was generated. This was performed with the aid of the mathematical software MATLAB (see Appendix 2 at http://cap-acp.org/ for the code script).

In order to test the potential improvement that the optimal grossing strategies noted above might have on tumour focus detection, a series of computer simulations were performed to test each grossing technique relative to the other (see code script from Appendix 3 at http://cap-acp.org/). It was surmised that the optimal grossing method should more frequently permit transection of a hypothetical tumour focus, thus closely approximating the likelihood the tumour focus will be detected on histological examination. In each simulation, 1,000 mathematically modelled lymph nodes were created with random measurements obtained using MATLAB's built-in random number generator. This number of lymph nodes per simulation, by the law of averages, should adequately account for most possible lymph node sizes as set forth in the matrix of lymph node sizes above. In each lymph node, a focus of metastasis was simulated and assigned a random location (excluding the lymph node's surface) and random size (<0.2 mm to limit the discussion to tumour foci smaller than micrometastases). The program actively excluded a node that was exactly spherical since, in such a case, the computer would be unable to discern an optimal grossing technique. The lymph node then underwent simulated grossing with cuts parallel either to the long axis or short axis starting from the centre and moving out. The program then determined which of the two methods was optimal based on the above calculations, calculated whether a grossing cut using either method would transect the tumour focus, and tallied

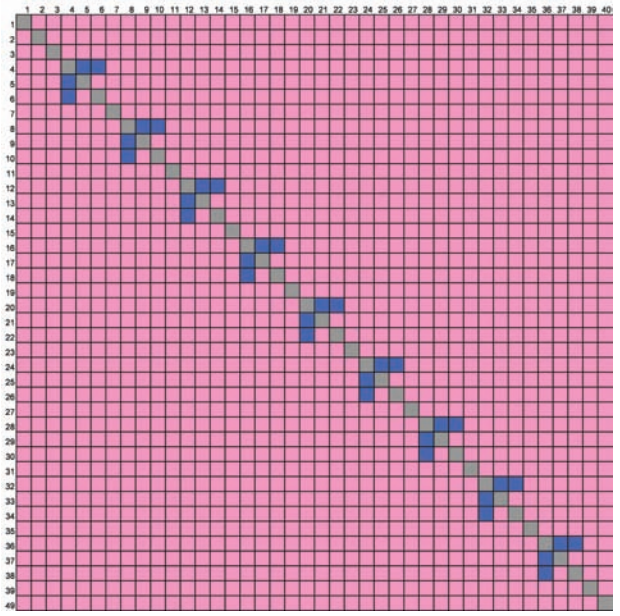

Figure 3. A 40 × 40 matrix of lymph node measurements; pink indicates optimal long axis approach, blue indicates optimal short axis approach, and grey indicates no difference in taking either approach.

whether the optimal method, the non-optimal method, or either method worked best. The simulations were repeated a total of 1,000 times to permit the generation of statistical data.

Results

By comparing the total optimal surface area for each of the short axis and long axis approaches, a 40 × 40 diagonally symmetric matrix was generated. As Figure 3 indicates, of the 820 unique lymph node sizes, the long axis approach (pink) was optimal in 802 cases (98%). The remaining cases were either equivalent by either approach (grey) or showed optimal surface area using the short axis approach (blue). Furthermore, a specific pattern of repetition was noted in the few cases of short axis preference: the short axis technique was preferred when the long and short axes had measurements 4n + 1 and 4n, respectively, or 4n+2 and 4n, respectively (for $n \geq 1$).

One thousand simulations, with 1,000 simulated lymph nodes each, were conducted with each node bearing a randomly positioned and sized tumour deposit (smaller than a microfocus). An average of 87.7 lymph node tumour foci showed grossing transection using the optimal approach; an average of 86.7 lymph node tumour foci showed grossing transection using the non-optimal approach. The two-tailed *t*-test showed this to be a statistically significant difference of means (p =.010). Furthermore, on average 13.7 lymph nodes were found to be equivocal to either technique. Notably, the number of lymph nodes whose tumour focus was not transected by either grossing technique was quite high, averaging at 811.9 (81%). This latter result is in keeping with the previous studies in which the frequency of missed tumour foci increased when the size cutoff was reduced.[5]

Discussion

Although debate persists as to the extent to which efforts to identify low-volume tumour foci in sentinel and non-sentinel lymph nodes should proceed, on a case-by-case basis, most pathologists will be loath to miss a metastasis, however small. Research into the best-practice handling of lymph nodes persists, and the focus of this research tends to be centred on maximizing the efficiency of histological and ancillary techniques at detecting metastatic foci, with the caveat that, from a practical perspective, a lymph node cannot be fully and completely examined microscopically. Little research has examined the manner in which a lymph node is grossed, however, and its potential impact on maximizing the detection of metastases.

The present study uses a mathematical model of a lymph node to calculate the maximum optimal cut surface area available for histological examination when the grossing technique is varied from either parallel to the long axis or parallel to the short axis. A comparison of these two approaches reveals that the optimal grossing technique is the long axis approach in 98% of simulated lymph nodes of varying sizes. In the great majority of cases, therefore, the approach described as optimal by Weaver and others is sound. A small number of predictable cases, however, do seem to show optimal grossing using the short axis approach, as described above. Nonetheless, when a simulation of mathematically modelled lymph nodes is performed to test the optimal and non-optimal grossing techniques head to head, only a marginal improvement in theoretical detection is noted, although this is statistically significant.

A "real-life" study to verify the above conclusions would be ideal but is highly unlikely. The resources required to adequately study even one lymph node in its entirety are a significant impediment. Furthermore, as pointed out in Weaver's application of the Heisenberg uncertainty principle, real-life limitations make the impact of an individual lymph node's questionable diagnosis of benignity impossible to assess; simulation, therefore, is the only plausible mode of study in this vein. The current study appears to be the strongest evidence thus far supporting the lymph node grossing practices described by Weaver et al.[5]

References

1. Edge S, Byrd DR, Comptom CC, et al. Purposes and principles o f cancer staging. In: AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010:3–14.
2. Tan JT, Bagnell M, Morgan JW, et al. The identification and treatment of isolated tumor cells reflect disparities in the delivery of breast cancer care. Am J Surg 2009;198:508–10.
3. Weaver DL. Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale. Mod Pathol 2010;23:S26–32.
4. Weaver DL. The prognostic importance of isolated tumor cell clusters and micrometastases in sentinel lymph nodes. Cancer Investig 2009;27:121–8.
5. Weaver DL, Krag D, Manna EA, et al. Detection of occult sentinel lymph node micrometastases by immunohistochemistry in breast cancer: an NSABP protocol B-32 quality assurance study. Cancer 2006;107:661–7.
6. Cserni G, Gregori D, Merletti F, et al. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg 2004;91:1245–52.
7. Park D, Karesen R, Naume B, et al. The prognostic impact of occult nodal metastasis in early breast carcinoma. Breast Cancer Res Treat 2009;118:57–66.
8. Saphir O, Amromin GD. Obscure axillary lymph node metastases in carcinoma of the breast. Cancer 1948;1:238–41.
9. Lester SC. Lymph nodes, spleen and bone marrow. In: Manual of Surgical Pathology, 3rd edition. Philadelphia (PA): Elsevier Saunders; 2010:513–24.
10. Shidham VB. Evaluation of sentinel lymph nodes for melanoma metastases by pathologists. Clin Plast Surg 2010;37:101–12.

Interpretation of Diagnostic Muscle Biopsies

Michael Farrell, FRCPI, FRCPC, FRCPath

ABSTRACT

This review of muscle biopsy interpretation is directed at surgical pathologists who are willing to take up the challenge. The approach to muscle biopsy interpretation follows an inside-out algorithm designed to achieve maximum diagnostic information from a well-prepared specimen, rather than providing the specific diagnostic label, which, even after detailed biochemical and genetic investigations, may elude even the most experienced myologists.

RÉSUMÉ

L'examen de l'interprétation des résultats de la biopsie musculaire s'adresse aux pathologistes spécialisés en pathologie chirurgicale qui sont disposés à relever le défi. La démarche d'interprétation est balisée par un algorithme conçu pour obtenir l'information diagnostique optimale du prélèvement effectué dans les règles, plutôt que pour déboucher sur le diagnostic précis, lequel peut échapper même au myologiste le plus chevronné après les analyses biochimiques et génétiques approfondies.

The past 10 years have witnessed spectacular advances in the characterization of many hitherto unclassified muscle disorders, largely due to an expanding range of antibodies directed against muscle membrane and sarcoplasmic targets.[1–4] At the outset, it is vital to stress that isolated specific diagnostic muscle biopsy appearances are rare. Instead, one tries to build a composite picture using a wide panel of stains and immunohistochemical reactions that allows a stratification of the biopsy into one of a small number of clinically relevant diagnostic categories (Table 1). Regular clinical-pathological muscle review meetings are essential for feedback, learning, and diagnosis refinement.

Choice of Biopsy Site and Transportation to Laboratory

Clinicians regularly seek advice from the laboratory on the optimum biopsy site and biopsy size. In patients with chronic muscle disease, it is best to avoid very weak muscles. Ultrasonography is useful for ensuring the muscle is not completely replaced by fat. In the absence of ultrasonography, a Medical Research Council (MRC) scale three-quarter strength muscle is preferred. If muscle disease is acute, a profoundly weak muscle is most likely to yield maximum diagnostic information. The gastrocnemius is best avoided as clinically irrelevant neuropathic change from lumbar spinal degenerative disc disease may be present, and this muscle often shows fatty replacement especially in patients with so-called calf hypertrophy. The decision to carry out open or needle biopsy is determined by operator experience, but considerable technical laboratory expertise is required to orientate the small muscle samples obtained by needle. Small sample size may limit the range of any additional investigations required, and some muscles, because of proximity to nerves and blood vessels, are unsuitable for needle biopsy. Obviously, injection or needle electromyography (EMG) sites must be avoided. At Beaumont Hospital, in Dublin, Ireland, we prefer open biopsy and recommend that a cylinder of muscle 5 × 10 mm be obtained. The muscle should be received in the laboratory within 2–3 hours of biopsy and is best transported on saline-moistened (not soaked) gauze without pinning or stretching. Even if delayed, it is still possible to obtain high-quality histochemistry for up to 24 hours, provided that muscle freezing, soaking, or exposure to formalin is avoided. It may be very helpful to

Michael Farrell is a consultant neuropathologist in the Department of Clinical Neurological Sciences at the Royal College of Surgeons in Ireland and Beaumont Hospital, in Dublin, Ireland. Correspondence may be directed to michaelfarrell@beaumont.ie.

This article has been peer reviewed.
Competing interests: None declared.

Table 1. Muscle Biopsy Interpretation: Category-Based Diagnosis

Normal

Uniform fibre size; zero inflammation, necrosis, fibrosis, and intact mosaic pattern on fibre typing.

End-Stage Muscle

Fat and fibrous tissue with rare muscle fibres.

i. Depending on history, might be suitable for membrane immunohistochemistry; otherwise, sign out as "inadequate specimen"

Neuropathic

Fibre atrophy: check fibre typing and determine if atrophy is one of the following:

i. Random – i.e., both fibres types involved
ii. Type specific
    1. Type 2 only: steroids – disuse
    2. Type 1 only: myopathy (see "Myopathic," below)

Inflammatory

Determine composition (T and B lymphocytes, eosinophils, and macrophages), distribution of infiltrate, and consider effects of previous modifiers, e.g., steroids. Inflammation may be patchy. Scrutinize non-inflammatory areas to eliminate underlying dystrophy. Proliferating sarcolemmal nuclei may simulate inflammation.

i. Targeted at fibres – polymyositis
ii. Perifascicular atrophy – dermatomyositis
iii. Not easily categorized – mixed connective tissue disease; check for myositis specific antibodies
iv. Fascial – fasciitis
v. Vessel based – vasculitis
vi. Think of IBM – but remember IBM is not an inflammatory disease

Dystrophic

Endomysial fibrosis; fibre necrosis with regeneration; variable inflammation (see discussion of fibre atrophy in "Neuropathic," above); central nucleation; fibre hypertrophy and splitting. Variable features include rods, cores, vacuoles, sarcoplasmic bodies, and ring fibres. Immunohistochemistry ± Western blot.

i. Sarcolemmal membrane
    1. Dystrophin
    2. Sarcoglycans
    3. Merosin
    4. Dysferlin
    5. Caveolin
ii. Sarcolemmal nuclei
    1. Emerin
    2. Lamin A/C
    3. Myotubular if many central nucleated fibres; also think of myotonic dystrophy
iii. Sarcoplasm
    1. Myofibrillar – cytoskeletal, structural
        a. Actinopathies, core disease, nemaline, telethionin, myosin heavy chain, desmin
iv. Ion channel/transporter (unlikely to be biopsied)
    1. Cl–; CA++; K+; Na+ ; ryanodine receptor; R-adenosinetriphosphatase

Myopathic

Fibre size variation; absence of main features in "End-Stage Muscle," "Neuropathic," and "Inflammatory," above. Histology dictated by speed of disease progression ranging from widespread fibre necrosis in acute rhabdomyolysis to minimal variation in fibre size in "non-specific minimal change myopathy." Look for ragged red fibres, cytochrome oxidase depletion and glycogen or lipid excess. Check myophosphorylase. Think of process.

i. Energy provision
    1. Glycogen metabolism; lipid transport and metabolism; mitochondrial structure, function and metabolism
ii. Drug induced
    1. Consider statins in every myopathy
        a. Vacuoles: amiodarone, colchicine, chloroquine cyclosporine, and drugs causing low K^+
        b. Ragged red fibres: zidovudine
        c. Type II fibre atrophy: steroids
        d. Neuropathic features: colchicine, chloroquine, and hydroxychloroquine
iii. Biopsy from intensive care – critical care myopathy/neuropathy
iv. Toxins
v. Infection
vi. Ischemic
    1. Compartment syndrome

orientate the muscle transversely using a dissecting microscope. Ice crystal artifact is avoided by dusting the muscle in talcum powder prior to immersion in liquid nitrogen. We do not find it necessary to use pre-cooled isopentane. A small portion of muscle is dissected and immersed in glutaraldehyde (prior to freezing) for electron microscopy (EM). The archived frozen tissue block is suitable for respiratory chain studies provided citrate synthase levels have not fallen too low. In general, formalin should be avoided, but when vasculitis or granulomatous disease is suspected, all of the muscle must be processed for microscopy. In this situation, we usually place any non-frozen muscle fragments in formalin for serial sectioning.

Reading the Biopsy: A Systematic Approach

Unless an orderly approach is adopted, one can easily miss important changes. It is vital to remind oneself that the muscle biopsy only provides a single snapshot of an evolving dynamic process. A well-stained hematoxylin and eosin (H & E) section often provides the key diagnostic information, which is subsequently endorsed by additional histochemical or

immunohistochemical stains. We favour an "inside out" approach in which fibres are examined first, followed in order by the endomysium, perimysium, and epimysium and lastly by the blood vessels.

Fibre Size

In the assessment of fibre size, care must be taken to ensure that the biopsy is orientated transversely. Oblique sectioning results in non-pathological fibre size variation. Physiological fibre size variation is found close to muscle fascia. In general, an absence of fibre size variation usually indicates minimal or no significant muscle disease.

The presence of randomly distributed atrophic angulated fibres is suggestive of early denervation, but confirmation of the random nature of fibre atrophy must be established (see below). Clusters of angulated atrophic fibres, (grouped atrophy) are diagnostic of denervation even without recourse to fibre typing. Fibre size variation may also be due to hypertrophy, a feature usually observed in the dystrophies. Hypertrophied fibres may undergo splitting, which exaggerates the degree of fibre size variation; but the split fibres are always of the same type as the parent hypertrophied fibre, which helps to distinguish split fibres from truly atrophic fibres. When atrophy is prominent at the edge of muscle fascicles, dermatomyositis (DM) should be considered, the perifascicular atrophy in this instance being attributed to peripheral fascicular ischemia secondary to small-vessel immune-mediated disease (Figure 1).

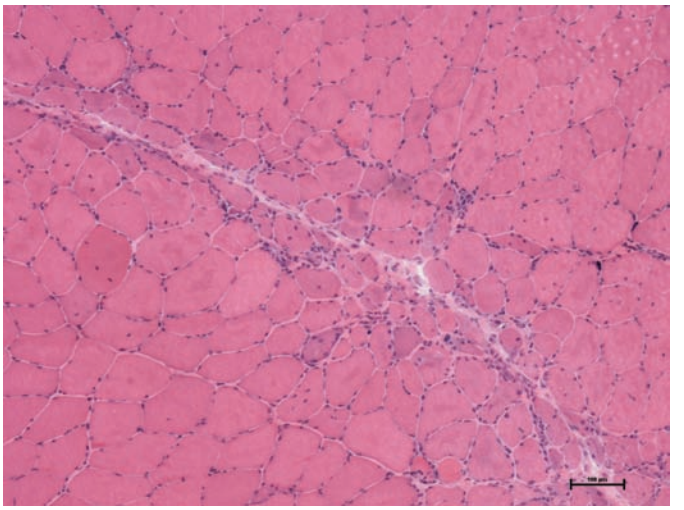

Figure 1. Perifascicular atrophy in the fibres located along the perimysial seam (top left to bottom right). (Hematoxylin and eosin)

Fibre typing is essential to determine if the atrophic process is random, that is, affecting both type I and II fibres, or selective. Random fibre atrophy is diagnostic of denervation without re-innervation. Selective type II fibre atrophy may be seen in disuse or following prolonged steroid therapy or sometimes in early denervation. Selective type I fibre atrophy is a feature of myotonic dystrophy and the congenital myopathies.[5]

An eyepiece graticule may be used to assess lesser fibre diameter. In general, precise measurement of fibre size is not necessary in adult muscle. In children, especially up to 3 years of age, it is advisable to calculate the mean lesser fibre diameter for at least 100 fibres. Diagnosis of denervation in these early years is difficult, and the implications of such a diagnosis is so serious that biopsies from children of this age should be processed in a centre that has experience in the interpretation of children's muscle biopsies. A mistaken diagnosis of spinal muscle atrophy (SMA) could result in withdrawal of life support systems from an infant whose muscle weakness and respiratory failure are incorrectly attributed to denervation. However, availability of rapid testing for the survival motor neurone (SMN) gene has replaced muscle biopsy as the first line of investigation in children with possible SMA.[6]

Re-innervation resulting in enlarged motor units and due to sprouting of distal intramuscular nerve terminals is a diagnostic feature of denervation on EMG and is identified microscopically as fibre type grouping. Antibodies to myosin heavy-chain fast and slow isoforms have been refined to the point where even fibres of intermediate type can be discerned using routine immunohistochemistry. Additionally, both antibodies are capable of identifying fibre types in formalin-fixed paraffin-embedded (FFPE) muscle. Normal fibre type distribution has a mosaic or checkerboard pattern. Loss of the mosaic pattern may be due to a predominance of one type over another, and in some muscles this is physiological. Fibre type grouping is the hallmark of re-innervation, and in our hands a group of fibres usually includes at least 16 fibres. Fibre grouping is also considered present if two touching fibres are completely surrounded on all sides by fibres of the same type. Grouping of both type I and type II fibres is essential for a definitive diagnosis of denervation. A diagnosis of denervation cannot be established when grouping involves one fibre type only, that is, the process is non-random.

Sarcolemmal Nuclei

As fetal muscle matures, sarcolemmal nuclei migrate to a peripheral location beneath the sarcolemmal membrane.

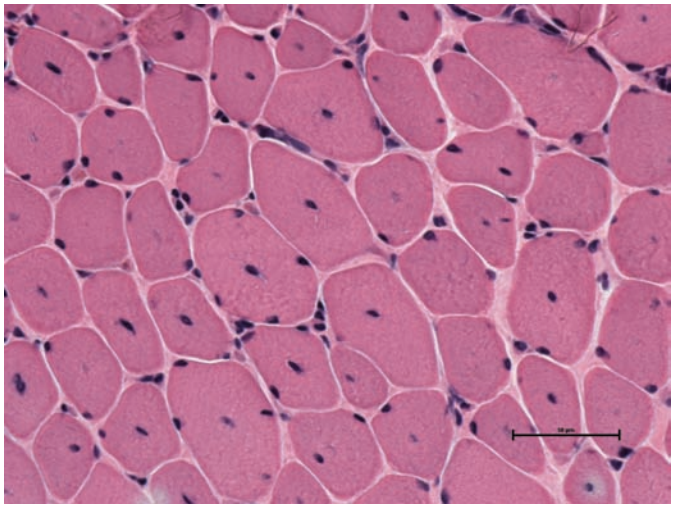

Figure 2. Virtually all fibres show central nucleation in this patient with myotubular myopathy. Note the slight increase in endomysial connective tissue. (Hematoxylin and eosin)

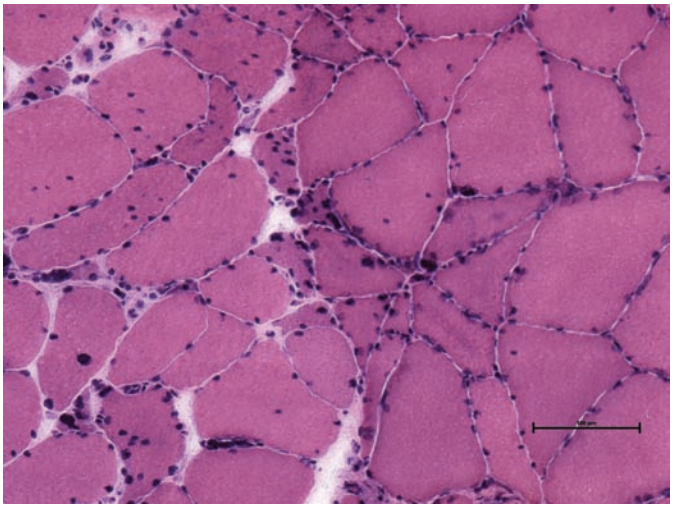

Figure 3. Angulated, atrophic fibres with very prominent sarcolemmal nuclei simulating an inflammatory infiltrate. (Hematoxylin and eosin)

Persistence of central nuclei is abnormal when more than 4% of fibres are involved. In myotubular myopathy, the vast majority of fibres have central-located nuclei, though a similar predominance of centrally nucleated fibres may be seen in myotonic dystrophy (Figure 2). Central nucleation is not specific and may be seen in chronic denervation, myopathy, and dystrophy. Increased numbers of sarcolemmal nuclei are frequent in atrophic fibres and may be exaggerated by the increased packing density associated with fibre atrophy (Figure 3). Perhaps the most common mistake in reading muscle biopsy is to interpret the densely packed, small, deeply basophilic nuclei as a lymphocytic infiltrate, but the issue is easily resolved by application of a lymphocytic marker such as CD45.

Sarcoplasm

Type I fibres are usually darker than type II fibres because of the increased numbers of mitochondria. Deeply basophilic sarcoplasm is typical of muscle fibre regeneration, which can be confirmed with fetal myosin immunohistochemistry. Regenerating fibres usually have large, pale vesicular nuclei.

Myofibre necrosis is, like many muscle biopsy appearances, non-specific. However, its histological recognition is critical. Sarcoplasmic pallor is suggestive of necrosis, and although necrosis is typically a feature of myopathy, it may also be present in acutely denervated muscle. As necrosis progresses, fibres become intensely eosinophilic and the integrity of the sarcolemmal membrane is compromised (Figure 4). Spectrin immunohistochemistry confirms membrane disruption. Later, necrotic fibres are replaced by macrophages, a finding that can easily be over-interpreted as evidence for a primary inflammatory process. The presence of several necrotic fibres lying close together suggests either a dystrophic process or perhaps a severe ischemic insult, provided non-necrotic fibres elsewhere look normal. Isolated spotty myofibre necrosis is more likely to reflect a toxic-metabolic process. Polymyositis (PM) and DM often have necrotic fibres as one element in an overall inflammatory process, the extent of which may have been modified by prior steroid therapy.[7,8] The relative prevalence of necrotic and regenerating fibres varies, depending on the phase of the primary disease process; for instance, myofibre regeneration may be minimal in late Duchenne's muscular dystrophy (DMD).

Sarcoplasmic Vacuoles

Pathological sarcoplasmic vacuolar change must be distinguished from ice crystal vacuoles, which are usually empty, non-membrane bound, and involve the entire muscle fascicle. Any sarcoplasmic structure may undergo dilatation and give rise to vacuoles. At light microscopic examination, it is not possible to differentiate between vacuolar change due to dilatation of the T tubules, sarcoplasmic reticulum, or lysosomes. Stains for lipid and glycogen help to determine the contents of vacuoles. Vacuoles may vary in size from single and

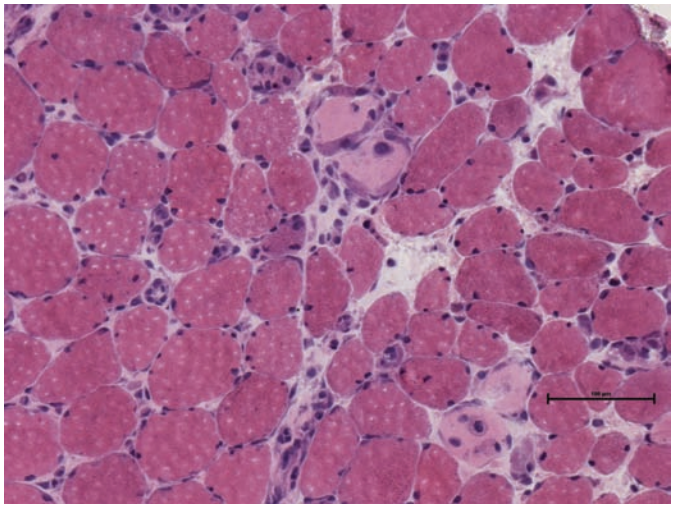

Figure 4. At least four necrotic fibres are present, and in all, there is peripheral sarcoplasmic basophilia, indicating early regeneration. Note the minor degree of ice crystal artifact in intact fibres. (Hematoxylin and eosin)

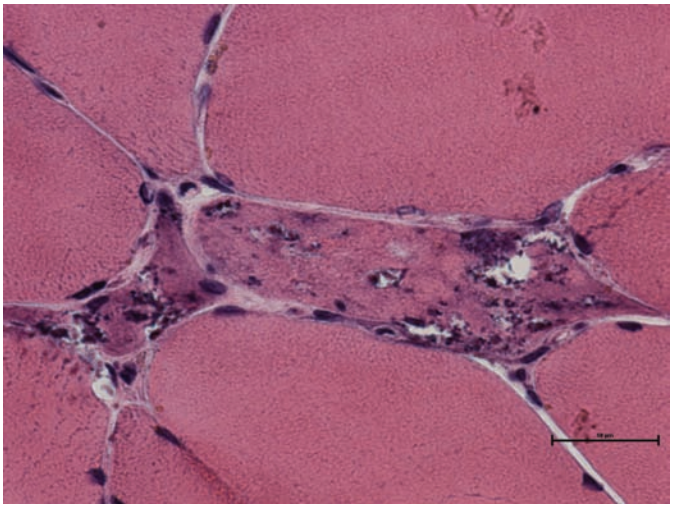

Figure 5. Rimmed vacuoles characterized by peripheral granular basophilic stippling in a patient with inclusion body myositis. (Hematoxylin and eosin)

large, for example, in hypokalemic periodic paralysis, to multiple and small, characteristic of lipid excess. Rimmed vacuoles (Figure 5) have an irregular configuration with increased peripheral staining using Gomori's modified trichrome (GMT). Large vacuoles, which react with acid phosphatase and periodic acid–Schiff (PAS) stain, are characteristic of acid maltase deficiency (Figure 6). The most frequently encountered vacuoles are autophagic vacuoles, which contain sarcoplasmic degradation products and are best demonstrated with acid phosphatase. These are non-specific indicators of muscle fibre degeneration.

Endomysium, Perimysium, and Epimysium

Inflammation and fibrosis are the two principal pathological findings in the endomysium, perimysium, and epimysium. Endomysial fibrosis is always abnormal and is a dominant feature of muscular dystrophy, especially congenital muscular dystrophy, but may also be seen in end-stage denervation and end-stage myopathy. Congenital muscular dystrophy, an imprecise term, refers to infants, weak from birth, often with contractures and usually with delayed motor milestones, and in whom a neurogenic cause has been excluded. Perimysial fibrosis is of lesser diagnostic importance, especially if not accompanied by endomysial fibrosis. An epimysial inflammatory infiltrate raises the possibility of fasciitis. Fascial inflammation may suggest eosinophilic fasciitis or eosinophilic myalgia syndrome.[9] When the inflammatory cells are centred on small endomysial vessels, DM is probable; when centred on individual myofibres, PM is likely (Figure 7). Lymphocytes dominate the inflammatory process in PM and DM with endomysial CD8+ T cells prominent in PM and B cells prominent in DM.[7,8] Demonstration of the complement membrane attack complex (MAC) C5b-9 in the vasculature favours DM rather than PM.[10,11] Steroid treatment and regional variability in disease expression may influence the intensity of the inflammatory infiltrate, and in some biopsies there may be little or no inflammation. In such situations, expression of sarcolemmal major histocompatibility complex (MHC) class I antigens provides supportive evidence of an immunological process at work.[12] Endomysial inflammation may occur in certain dystrophies, especially in facioscapulohumeral dystrophy.[13] Careful examination of fibres remote from the inflammation reveals other supportive dystrophic features not present in PM or DM. Great care must be taken to separate inclusion body "myositis" (IBM) from other true inflammatory myopathies. IBM is a degenerative rather than an immune-mediated disease, and it does not respond to steroids, which are actually contraindicated.[14,15] The temptation to lump all biopsies with an inflammatory component into a "myositis" category must be resisted and other supportive features of IBM sought – including rimmed vacuoles and elements of mitochondrial dysfunction such as cytochrome oxidase (COX) depletion and ragged red fibres (RRFs). A prominent eosinophilic component suggests a drug-induced myopathy,

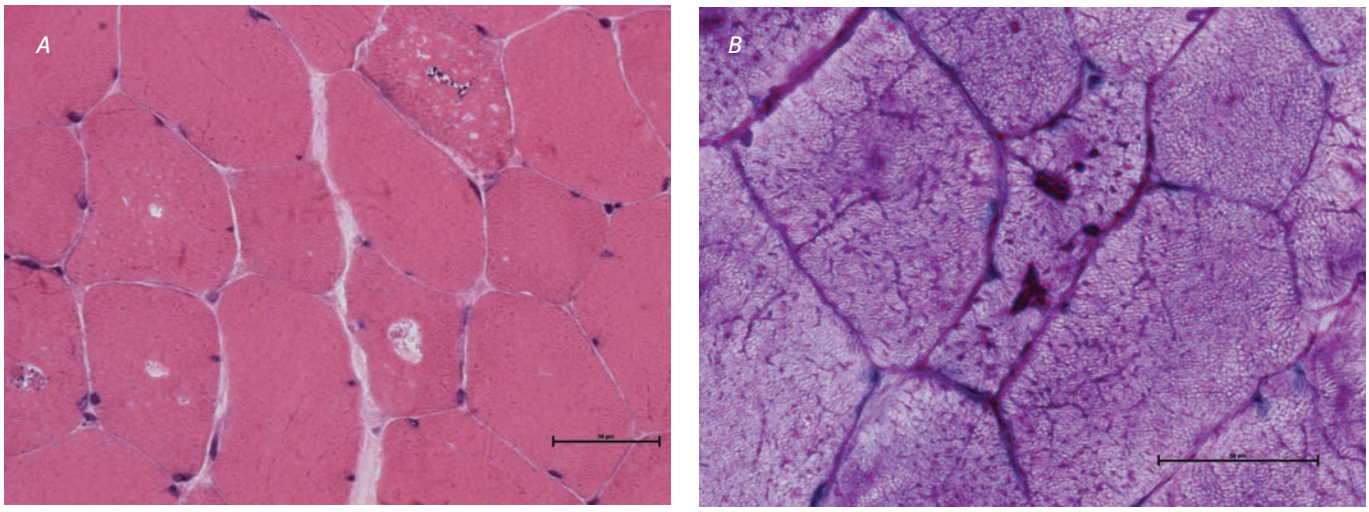

Figure 6. *A*, Acid maltase deficiency. Vacuolar change in which at least three centrally located non-rimmed vacuoles are present. Note the single-rimmed vacuole (top right of centre) (hematoxylin and eosin). *B*, The vacuoles seen in panel A are periodic acid–Schiff positive.

eosinophilic myalgia syndrome, or parasitic infestation. Myositis dominated by eosinophils should trigger an examination of multiple levels for the presence of parasitic larvae, especially trichinosis and cysticercosis. Foci of calcification and granulomatous inflammation may be all that remains. Granulomatous inflammation[16] suggests either tuberculosis or sarcoidosis.[17,18] *Mycobacterium avium-intracellulare* infection of muscle is described in human immunodeficiency virus infection.[19] Granulomas may be present in up to 60% of patients with sarcoid but are usually asymptomatic. Similarly, asymptomatic granulomas may be present in muscles obtained from patients with Crohn's disease. When an inflammatory biopsy is not easily characterized as either PM or DM, less common inflammatory disorders such as anti-synthetase syndrome should be considered and supported by screening for myositis-specific antibodies.[20,21]

Blood Vessels

A diagnosis of vasculitis is easy when classic features of vasculitis are present in an endomysial blood vessel. Typically, however, patients may already have been treated with steroids and the inflammatory process may be extremely patchy and vary in its severity and extent. Nevertheless, whenever a perivascular lymphocytic infiltrate encroaches on a vessel wall, vasculitis must be suspected. In polyarteritis nodosa, the infiltrate comprises lymphocytes, histiocytes, eosinophils, and neutrophils.[22] Frequently, the perivascular infiltrate is less pleocytic. Multiple levels must be examined and evidence of vessel wall destruction sought. Where tissue is available, demonstration of immune complexes in the vessels may be helpful.

Having carefully examined the H & E–stained section, one already has a firm view of the categories of muscle disease most appropriate for the biopsy findings: normal; atrophic process awaiting fibre typing; inflammatory awaiting characterization of the inflammatory infiltrate; dystrophic awaiting identification of deficient proteins in muscle membrane or myonuclei; and non-specific myopathic awaiting further characterization with special stains.

Special Stains

In a non-specialist laboratory, a combination of modified GMT, PAS with and without diastaste, oil red O, myosin immunohistochemistry, nicotinamide adenine dinucleotide dehydrogenase tetrazolium reductase (NADH-TR) and COX with or without succinic dehydrogenase (SDH) is adequate for most diagnoses.

Gomori' s Modified Trichrome

GMT is a capricious stain that is considered satisfactory when fine sarcoplasmic brown-red granular staining is observed. A well-executed GMT stain can be judged by its ability to allow a distinction between type I and type II fibres. RRFs are irregular, dark red-brown subsarcolemmal deposits representing an accumulation of mitochondria (either normal or abnormal) beneath the membrane and are typical of underlying

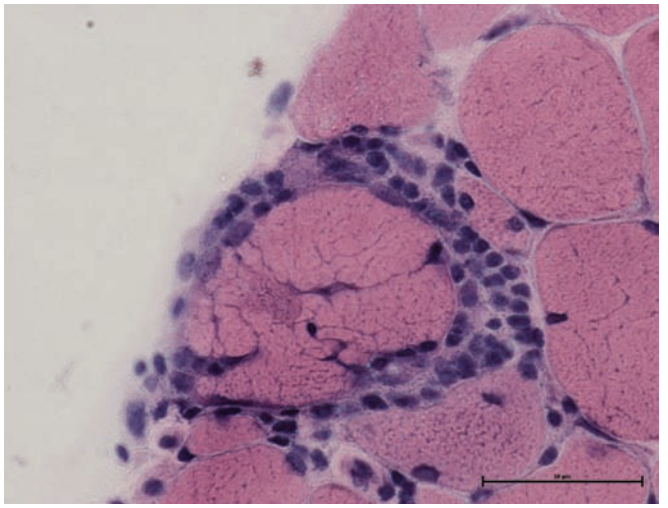

Figure 7. Polymyositis in which lymphocytes are targeted on and beginning to invade a single muscle fibre. (Hematoxylin and eosin)

mitochondrial dysfunction (Figure 8). Sometimes there is a mild increase in subsarcolemmal staining with GMT that is above normal but that has not yet resulted in RRF formation. The significance of this change remains to be determined. Further investigation for possible mitochondrial disease is a highly specialized task that includes analysis of respiratory chain function and mitochondrial deoxyribonucleic acid (mtDNA), as well as genes involved in mtDNA synthesis.[23–26] Archived frozen muscle is perfectly adequate for all of these specialized studies. RRF must be distinguished from tubular aggregates, which also accumulate in the subsarcolemmal location and stain red with GMT. Tubular aggregates do not have the ragged appearance of RRF, and their tubular structure is readily evident on electron microscopy (EM). They are not specific for any disease process.

Though nemaline rods are said to stain red with GMT, they are usually so dark that it becomes impossible to say whether they are dark green or maroon. Typically located in the subsarcolemmal zone, they vary in number and distribution (see Figure 9 at http://cap-acp.org/). EM shows continuity between the rods and the Z lines. Rods are diagnostic of nemaline myopathy, a heterogenous condition that may be congenital, with up to seven forms identified.[27–29] In the most common form, α-actin accumulates in the rods and mutations in the *ACTA1* gene must be sought. Sporadic forms of nemaline myopathy range from a congenital, rapidly fatal form through to a non-progressive adult form with minimal disability. In the majority of these sporadic forms, the rogue muscle protein has not been identified. Rarely isolated rods may occur in the absence of any significant muscle disease.

Periodic Acid–Schiff Stain

The assessment of glycogen content of muscle is difficult as there can be tremendous variation in the staining intensity of the routine PAS stain. Like GMT, a satisfactory PAS allows separation of type I and type II fibres. Acid maltase deficiency (type II glycogenosis) is characterized by a variable number of PAS-positive vacuoles (see Figure 6).[30] Acid phosphatase activity is prominent close to the vacuoles. In McArdle disease (type V glycogenosis), glycogen accumulation may be minimal; and unless myophosphorylase staining is carried out routinely, the diagnosis of McArdle disease is missed. The normal myophosphorylase reaction fades quickly but not in blood vessels, which serve as an internal control. Normal muscle should also be included as a control. Nevertheless, the freshly stained section should be examined immediately; the absence of myophosphorylase except in blood vessels establishes the diagnosis. The glycogen storage disorders usually present with exercise intolerance or muscle cramps and fatigue and must always be included in the differential diagnosis of myoglobinuria.

Oil Red O

Large droplets overlying muscle fibres are frequently encountered with oil red O but are of no significance. Typically, sarcoplasmic lipid is visible as small droplets. Excess lipid may be present in muscle as a result of obesity, but the lipid that accumulates because of dysfunctional lipid transportation across membranes (carnitine or carnitine palmityltransferase deficiency), defective acyl-coenzyme A dehydrogenase, or reduced functionality of the respiratory chain is typically intense, striking, and not easily missed (see Figure 10 at http://cap-acp.org/).[31] Confirmation of lipid excess by EM prompts an investigation of fatty acid metabolism, which is best carried out in a specialist metabolic unit.

Nicotinamide Adenine Dinucleotide Dehydrogenase Tetrazolium Reductase

The NADH-TR stain should not be used for assessment in fibre type differentiation as blurring of the distinction between type I and type II fibres may be present. This stain is very useful for the assessment of mitochondrial myopathies, where increased subsarcolemmal staining represents an accumulation of

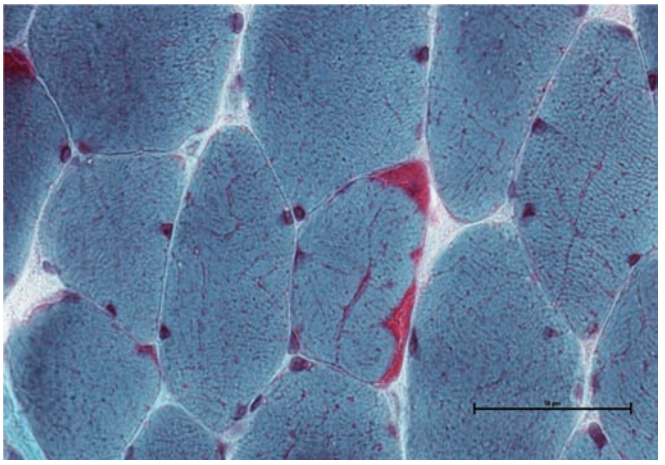

Figure 8. Mitochondrial myopathy characterized by ragged red fibre highlighted by staining with Gomori's modified trichrome.

mitochondria corresponding in location to the RRFs (ragged blue fibres). The use of NADH-TR is the method of choice for the demonstration of cores, the hallmark of core myopathy.[32,33] Tubular aggregates are also characterized by increased subsarcolemmal staining. Where it is difficult to establish a diagnosis of denervation with immunocytochemistry, the presence in the NADH-TR stain of small, darkly stained, angulated fibres or of target fibres provides supporting evidence for denervation. Patchy loss of myofibrillary meshwork on the NADH-TR reaction, when frequent, suggests a myopathic process. Lobulated fibres due to clustering of mitochondria are identified using NADH-TR and, though not specific, are suggestive of mitochondrial dysfunction (see Figure 11 at http://cap-acp.org/).

Cytochrome Oxidase with Succinic Dehydrogenase

Diminished COX staining may prove difficult to assess, but when COX is combined with SDH (nuclear encoded), fibres deficient in COX will, through activation of the mitochondria-to-nucleus feedback loop, appear blue as a result of increased activation of the nuclear-encoded SDH (see Figure 12 at http://cap-acp.org/). The COX-SDH is an excellent screen for mitochondrial dysfunction.[34,35] Apart from the many well-characterized mitochondrial disorders affecting muscle, COX depletion may be acquired as result of normal aging and may be seen in IBM or in patients in receipt of cholesterol-lowering drugs.

Immunohistochemistry

As previously stated, immunocytochemistry has replaced adenosinetriphosphatase-based histochemistry for fibre typing and can be easily carried out in a non-specialist laboratory. Antibodies are available for virtually all of the proteins in sarcoplasm, muscle membrane, and extracellular matrix, but only some are required for day-to-day practice.[36,37] Demonstration of a membrane protein deficiency usually requires confirmation by Western blot in a specialist muscle protein laboratory. Automated immunohistochemistry reduces workload and day-to-day variability in staining. We favour the Bond Polymer Detection Kit with a diamin-obenzidine chromogen. Others favour fluorescence-based antibodies that, it is claimed, are more sensitive in demonstrating minor changes in antigen expression. The development of close links with the regional muscle protein laboratory is essential for feedback of the results of Western blot studies.

Spectrin

It is always advisable to assess the integrity of muscle membranes with spectrin; otherwise, "false-positive" immunostaining is obtained with necrotic or pre-necrotic fibres (see Figure 13 at http://cap-acp.org/). The pattern of membranous immunostaining with spectrin is virtually identical to the normal dystrophin, sarcoglycan (SG), dystroglycan (DG), and merosin staining.

Dystrophin

Antibodies to the NH_2, COOH, and rod components of the dystrophin molecule must be used (see Figure 14 at http://cap-acp.org/). In DMD, there is usually a complete absence of staining with each antibody in all of the fibres, reflecting a complete disruption of the DMD gene reading frame.[38] Occasional immunopositive revertant fibres may be seen and reflect a correction of the reading frame with some, albeit abnormal, dystrophin expression (see Figure 15 at http://cap-acp.org/). In Becker's muscular dystrophy, the DMD gene reading frame is intact, and there is great variation in the extent of dystrophin staining with a majority of fibres showing some staining, albeit reduced.

Sarcoglycans α, β, γ, and δ

Deficiencies in the SGs comprise the largest group of recessively inherited limb girdle dystrophies.[39] Because of the pivotal transmembranous position of the SGs, the loss of one SG may lead to the secondary loss of other SGs, and indeed secondary SG loss may also be observed in DMD. It is crucial that any diminution

of SG staining be verified with a Western blot. Although we use the four SG antibodies, careful evaluation of just two (α and β) is probably sufficient for the needs of most laboratories.

Dystroglycans α and β

The α and β DGs occupy a pivotal position linking the muscle membrane with the extracellular matrix, and of the two, αDG is the more important. However, sourcing a reliable αDG antibody capable of giving reproducible results is difficult. Both DGs are encoded by the *DAG1* gene, but *DAG1* mutations are exceptionally rare as a cause of muscle disease. However, glycosylation is a key event in normal αDG function, and an increasing number of congenital muscular dystrophies are due to genetically determined defects in αDG glycosylation.[40,41] Because of the widespread distribution of αDG in other organs, this group of congenital muscular dystrophies is often characterized by structural changes in the brain or eye.

Merosin (Laminin α2)

Merosin is a heterotrimer composed of laminin subunits α2, β1, and γ1 and is the main laminin found in muscle fibres.[42,43] Of the extracellular matrix proteins linked to αDG, merosin is the most important, and its absence is characterized by severe congenital muscular dystrophy in which affected children have profound weakness often with contractures, seizures ,and changes in cerebral white matter reflective of delayed myelin maturation. As merosin is widely expressed, merosin staining of the skin may obviate the need for muscle biopsy.

Dysferlin

Located in apparent isolation in the muscle membrane, dysferlin has major role to play in the repair of muscle membrane defects, and this can be reflected in alterations in the distribution of immunolabelled dysferlin so that instead of nice linear membranous staining, sarcoplasmic expression may be observed with or without reduced membranous staining.[44,45] Interpretation of dysferlin immunopositivity may be challenging, and, as with other muscle proteins but particularly with dysferlin, it is essential that confirmatory Western blot be carried out. Over 300 mutations in the *DYSF* gene have been reported, and the clinical expression of these is highly variable, with distal muscle involvement a frequent finding.

Caveolin

Encoded by the CAV3 gene, caveolin, like its near neighbour dysferlin, is fixed in the muscle membrane caveolae remote from the main dystrophin-dystroglycan-laminin complex and, as with dysferlin, it may play a role in membrane repair.[46] Normal labelling of caveolin-3 is membranous just like spectrin, but indentation of the sarcolemmal membrane, reflecting localization in caveolae, is often observed. Defective caveolin function is associated with an unusual cluster of muscle disorders that includes rippling muscle disease and distal myopathy and should also be considered in patients with persistent creatine kinase–emia.

Emerin

Emerin contrasts with the other membranous proteins described above in that it is expressed in myonuclei (see Figure 16 at http://cap-acp.org/) together with lamin A/C. Encoded respectively by the *EDMD1* gene on Xq28 and the *EDMD2* gene on chromosome 1q21.2, these myonuclear myopathies are characterized by early contractures, often before much weakness has developed, and by frequent cardiac involvement.[47,48] Normal myonuclear staining is easily assessed, but muscle pathology is highly variable, with some patients even showing features indistinguishable from IBM.

Desmin and Myofibrillar Myopathy

Encoded by the *DES* gene on chromosome 2q35, desmin, as all surgical pathologists are aware, is a muscle-specific, intermediate filament protein present in all muscle types. What surgical pathologists may not realize is that mutations in the *DES* gene may give rise to an increasingly important group of myofibrillary myopathies characterized by huge clinical variability and by accumulation of immunopositive desmin in muscle (see Figure 17 at http://cap-acp.org/),[49,50] Predictably, cardiac muscle involvement with arrhythmias and conduction block is frequent and may lead to sudden death. Distal involvement may simulate peripheral nerve disease. Many myofibrillary myopathies are not desmin-related, and in such desmin-negative cases, labelling with αβ-crystallin and myotilin may confirm the identity of the sarcoplasmic hyaline material.

Conclusion

Reading a muscle biopsy is not difficult provided the biopsy has been well prepared and observations are made carefully and systematically. It may be difficult to arrive at "the definitive diagnosis" until the biopsy is discussed with the clinician. Even after discussion, a definitive diagnosis may depend on

additional specialist investigations and provided the biopsy has been processed speedily and carefully, these can be accomplished. The laboratory methods required for optimum preparation of a muscle biopsy are detailed in the third edition of the classic seminal work on muscle biopsy by Dubowitz and Sewry.[51]

References

1. Muntoni F, Voit T. The congenital muscular dystrophies in 2004: a century of exciting progress. Neuromuscul Disord 2004;14:635–49.
2. Sewry CA, Jimenez-Mallebrera C, Muntoni F. Congenital myopathies. Curr Opin Neurol 2008;21:569–75.
3. Muntoni F, Guicheney P, Voit T. 158th ENMC international workshop on congenital muscular dystrophy (Xth international CMD workshop) 8th–10th February 2008, Naarden, The Netherlands. Neuromuscul Disord 2009;19:229–34.
4. Sewry CA. Immunocytochemical analysis of human muscular dystrophy. Microsc Res Tech 2000;48:142–54.
5. Laing NG. Congenital myopathies. Curr Opin Neurol 2007;20:583–9.
6. Farrar MA, Johnston HM, Grattan-Smith P, et al. Spinal muscular atrophy: molecular mechanisms. Curr Mol Med 2009;9:851–62.
7. Bornemann A, Heitmann S, Lindner A. Myositides. Pathologe 2009;30:352–6.
8. Mammen AL. Dermatomyositis and polymyositis: clinical presentation, autoantibodies, and pathogenesis. Ann N Y Acad Sci 2010;1184:134–53.
9. Varga J, Kähäri VM. Eosinophilia-myalgia syndrome, eosinophilic fasciitis, and related fibrosing disorders. Curr Opin Rheumatol 1997;9:562–70.
10. Sakuta R, Murakami N, Jin Y, et al. Diagnostic significance of membrane attack complex and vitronectin in childhood dermatomyositis. J Child Neurol 2005;20:597–602.
11. Greenberg SA. Inflammatory myopathies: disease mechanisms. Curr Opin Neurol 2009;22:516–23.
12. Sallum AM, Kiss MH, Silva CA, et al. MHC class I and II expression in juvenile dermatomyositis skeletal muscle. Clin Exp Rheumatol 2009 ;27:519–26.
13. Padberg GW, van Engelen BG. Facioscapulohumeral muscular dystrophy. Curr Opin Neurol 2009;22:539–42.
14. Askanas V, Engel WK, Nogalska A. Inclusion body myositis: a degenerative muscle disease associated with intra-muscle fiber multi-protein aggregates, proteasome inhibition, endoplasmic reticulum stress and decreased lysosomal degradation. Brain Pathol 2009;19:493–506.
15. Amato AA, Barohn RJ. Inclusion body myositis: old and new concepts. J Neurol Neurosurg Psychiatr 2009;80:1186–93.
16. Le Roux K, Streichenberger N, Vial C, et al. Granulomatous myositis: a clinical study of thirteen cases. Muscle Nerve 2007;35:171–7.
17. Yamada H, Ishii W, Ito S, et al. Sarcoid myositis with muscle weakness as a presenting symptom. Mod Rheumatol 2007;17:243–6.
18. Wrzolek MA, Rao C, Kozlowski PB, Sher JH. Muscle and nerve involvement in AIDS patient with disseminated Mycobacterium avium-intracellulare infection. Muscle Nerve 1989;12:247–9.
19. Wrzolek MA, Sher JH, Kozlowski PB, Rao C. Skeletal muscle pathology in AIDS: an autopsy study. Muscle Nerve 1990;13:508–15.
20. Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford) 2009;48:607–12.
21. Mimori T, Imura Y, Nakashima R, Yoshifuji H. Autoantibodies in idiopathic inflammatory myopathy: an update on clinical and pathophysiological significance. Curr Opin Rheumatol 2007;19:523–9.
22. Lupoli S, Gargiulo A, Rossi R, Ames PR. Myositis as a presenting feature of polyarteritis nodosa. Clin Exp Rheumatol 2004;22:507–8.
23. McFarland R, Taylor RW, Turnbull DM. Mitochondrial disease--its impact, aetiology, and pathology. Curr Top Dev Biol 2007;77:113–55.
24. Tuppen HA, Blakely EL, Turnbull DM, Taylor RW. Mitochondrial DNA mutations and human disease. Biochim Biophys Acta 2010;1797:113–28.
25. Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nat Rev Genet 2005; 6:389–402.
26. Filosto M, Tomelleri G, Tonin P, et al. Neuropathology of mitochondrial diseases. Biosci Rep 2007;27:23–30.
27. Laing NG, Wallgren-Pettersson C. 161st ENMC International Workshop on nemaline myopathy and related disorders, Newcastle upon Tyne, 2008. Neuromuscul Disord 2009;19:300–5.
28. Fernandez C, Figarella-Branger D, Meyronet D, et al. Electron microscopy in neuromuscular disorders. Ultrastruct Pathol 2005;29:437–50.
29. Ochala J. Thin filament proteins mutations associated with skeletal myopathies: defective regulation of muscle contraction. J Mol Med 2008;86:1197–204.
30. DiMauro S, Bruno C. Glycogen storage diseases of muscle. Curr Opin Neurol 1998;11:477–84.
31. Bruno C, DiMauro S. Lipid storage myopathies. Curr Opin Neurol 2008;21:601–6.
32. Sewry CA, Müller C, Davis M, et al. The spectrum of pathology in central core disease. Neuromuscul Disord 2002;12:930–8.
33. Quinlivan RM, Muller CR, Davis M, et al. Central core disease: clinical, pathological, and genetic features. Arch Dis Child 2003;88:1051–5.
34. DiMauro S, Lombes A, Nakase H, et al. Cytochrome c oxidase deficiency. Pediatr Res 1990;28:536–41.
35. Sciacco M, Bonilla E. Cytochemistry and immunocytochemistry of mitochondria in tissue sections. Methods Enzymol 1996;264:509–21.
36. Brown SC, Torelli S, Jimenez C, et al. Immunopathology and molecular genetics of dystrophinopathies. Suppl Clin Neurophysiol 2004;57:313–21.
37. Sewry CA. Immunocytochemical analysis of human muscular dystrophy. Microsc Res Tech 2000;48:142–54.
38. Bushby K, Finkel R, Birnkrant DJ, et al., DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010;9:77–93.
39. Bushby K. Diagnosis and management of the limb girdle muscular dystrophies. Pract Neurol 2009;9:314–23.
40. Muntoni F, Torelli S, Brockington M. Muscular dystrophies due to glycosylation defects. Neurotherapeutics 2008;5:627–32.
41. Brockington M, Muntoni F. The modulation of skeletal muscle glycosylation as a potential therapeutic intervention in muscular dystrophies. Acta Myol 2005;24:217–21.
42. Mercuri E, Longman C. Congenital muscular dystrophy. Pediatr Ann 2005;34:560–2, 564–8.
43. Jimenez-Mallebrera C, Brown SC, Sewry CA, Muntoni F. Congenital muscular dystrophy: molecular and cellular aspects. Cell Mol Life Sci 2005;62:809–23.
44. Han R, Campbell KP. Dysferlin and muscle membrane repair. Curr Opin Cell Biol 2007;19:409–16.
45. Bansal D, Campbell KP. Dysferlin and the plasma membrane repair in muscular dystrophy. Trends Cell Biol 2004;14:206–13.
46. Gazzerro E, Sotgia F, Bruno C, et al. Caveolinopathies: from the biology of caveolin-3 to human diseases. Eur J Hum Genet 2010;18:137–45.
47. Sewry CA, Brown SC, Mercuri E, et al. Skeletal muscle pathology in autosomal dominant Emery Dreifuss muscular dystrophy with lamin A/C mutations. Neuropathol Appl Neurobiol 2001;27:281–90
48. Brown SC, Piercy RJ, Muntoni F, Sewry CA. Investigating the pathology of Emery-Dreifuss muscular dystrophy. Biochem Soc Trans 2008;36:1335–8.
49. Goebel HH, Fardeau M, Olivé M, Schröder R. 156th ENMC International Workshop: desmin and protein aggregate myopathies, 9–11 November 2007, Naarden, The Netherlands. Neuromuscul Disord 2008;18:583–92.
50. Schröder R, Schoser B. Myofibrillar myopathies: a clinical and myopathological guide. Brain Pathol 2009;19:483–92.
51. Dubowitz V, Sewry CA. Muscle Biopsy: A Practical Approach, 3rd edition. Saunders Elsevier; 2007.

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