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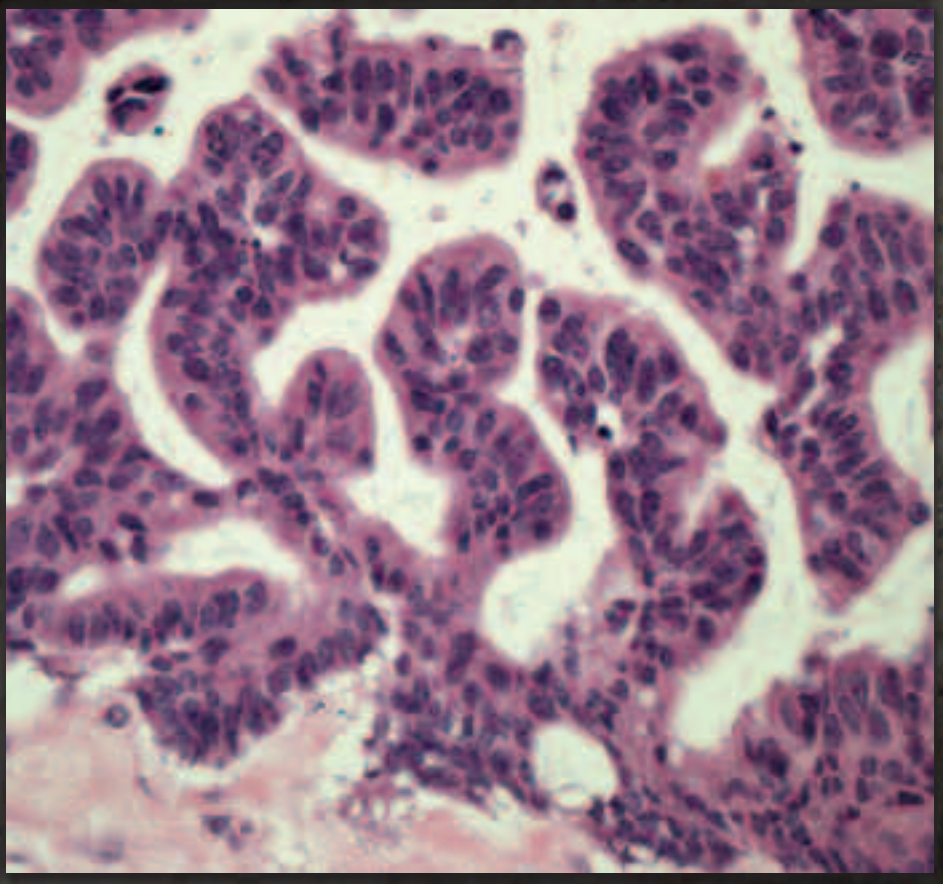

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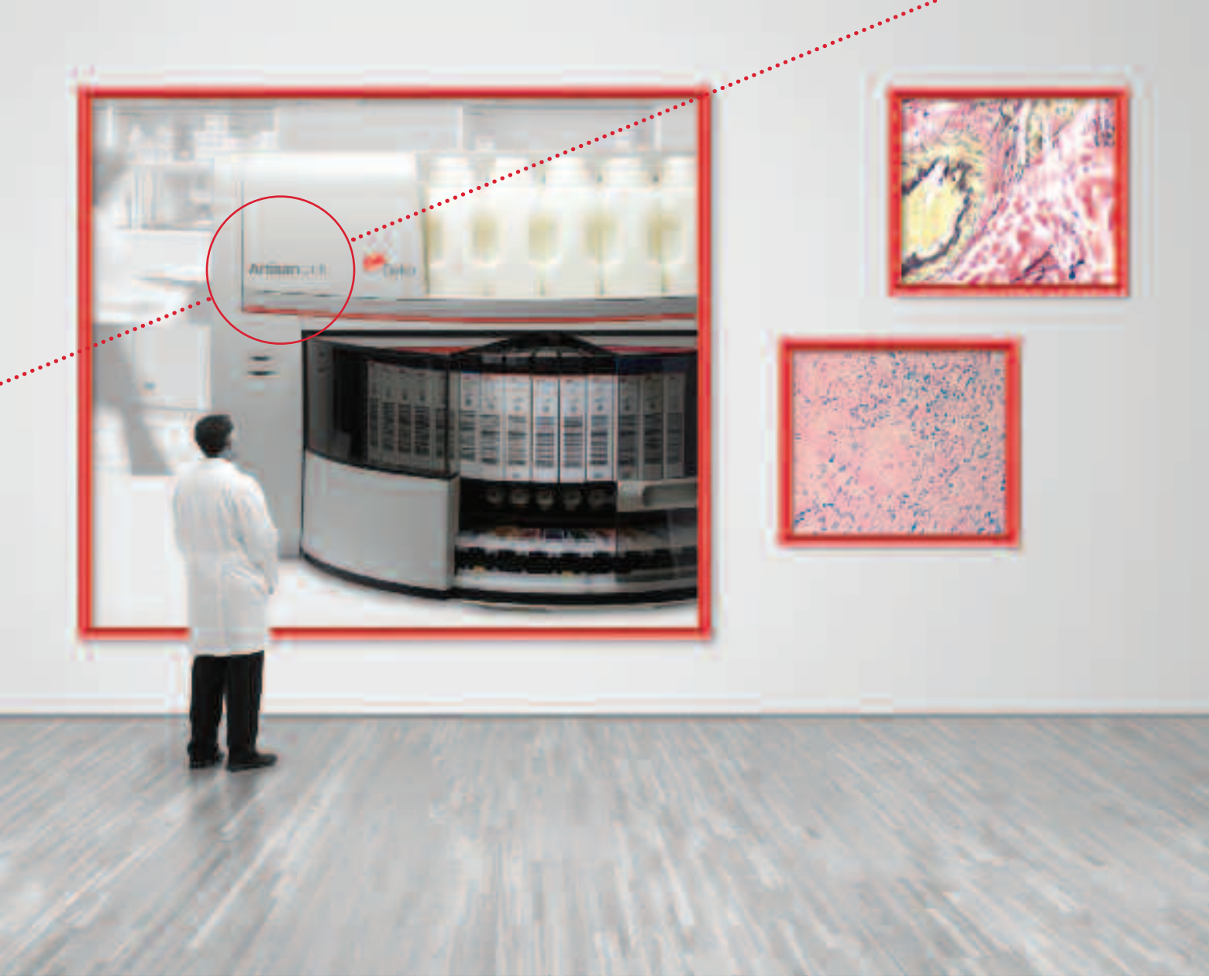

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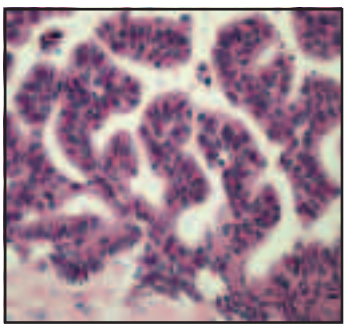

This image shows a pancreatobiliary-type intraductal papillary mucinous neoplasm.

EDITORIAL

Cytopathology in Canada: A Morphological Field in Metamorphosis

One would have had to be living in a cocoon not to notice that the field of cytopathology is changing. We know that changes are looming for gynecological cytology resulting from the implementation of the human papillomavirus (HPV) vaccination in Canada, and this topic will be addressed in an upcoming issue of *The Canadian Journal of Pathology (CJP)*. In this editorial, I would like to outline several other changes impacting cytopathology.

The relatively new techniques of endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA) and endoscopic ultrasound-guided FNA (EUS-FNA) have gained momentum.[1–5] Compared with the long-established transtracheal or transbronchial (Wang) needle aspiration, which is obtained "blindly" via a flexible bronchoscope and which provides a restricted sampling of large subcarinal lymph nodes, EBUS-FNA is more precise because it is performed under visual guidance with a novel endobronchoscope equipped with a needle. EBUS-FNA results in a higher diagnostic yield than the traditional technique (85% versus 66%) and also allows a much wider mediastinal sampling. EUS-FNA, performed by gastroenterologists during endoscopy, can also sample paraesophageal and inferior mediastinal lymph nodes via the esophagus; it is most often used, however, to detect and stage gastrointestinal and pancreatic neoplasms. Most challenging to cytopathologists are the cystic pancreatic lesions that require integration of imaging, clinical, and biochemical data with the cytological findings. While these newer techniques sample a wider spectrum of lesions, they also create a new set of pitfalls in interpretation of which the cytopathologist must be aware.

Ultrasound (US) has also had an important impact on thyroid FNAs in recent years. Although palpation-directed thyroid FNAs are still acceptable, an increasing number are being done under US guidance because recent guidelines from the American Thyroid Association recommend that all patients with palpable nodules undergo a dedicated thyroid US examination.[6,7] Although US-guided thyroid FNAs used to be entrenched in the radiologists' domain, an increasing number of endocrinologists and head and neck surgeons now perform them because the technique is relatively easy to learn. Some cytopathologists are also performing them now. It is an area of potential expansion for pathology, particularly in places where the supply of pathologists is sufficient to meet all the demands put on them.

As with many areas of surgical pathology, cytopathology has benefited from standardization of terminology. Following the Bethesda reporting system for gynecological cytology, there is now a Bethesda system for thyroid cytopathology.[8] Although likely to evolve, this is a definite step toward putting order into the chaotic reporting of thyroid FNA diagnoses. It will facilitate the comparison of data between institutions and ensure a better understanding of our reports by clinicians and a more standardized approach to the follow-up of lesions, in particular equivocal ones. For example, a repeat FNA is suggested for those classified as "atypia of undetermined significance" because the majority of these are due to scanty specimens.

The explosion of molecular diagnostics in pathology has not missed cytopathology because cytology specimens are often sufficient and suitable for these ancillary studies. In particular, there is an exponential growth in the use of fluorescence in situ hybridization (FISH) in cytological specimens (e.g., UroVysion for urine samples).[9] There is also a growing interest in integrating molecular data to refine equivocal diagnostic categories by looking for chromosomal translocations such as *RET/PTC, PAX8/PPARγ*, or *BRAF* mutations in cases of "atypia of undetermined significance" in thyroid FNAs.[10]

Standardization and validation of immunocytochemistry on cytological specimens, particularly for predictive markers, are becoming very important. Since most cytology specimens are collected in alcohol-based fixatives, as opposed to the formalin-fixed specimens used in most procedures in immunohistochemistry laboratories, selection and validation of appropriate controls are imperative.[11] Guidance from the Canadian Association of Pathologists–Association canadienne des pathologistes (CAP-ACP) immunohistochemistry group in this matter would be welcome.

As pointed out in a recent *CJP* editorial,[12] informatics is playing an increasingly important role in pathology. Informatics is impacting on cytopathology in many ways, including digital imaging,[13] whole slide scanning for diagnostic "telecytology"[14] or continuing education, standardization of reporting (i.e., use of "canned" diagnoses), and as a powerful quality assurance tool to retrieve data and performance indicators.

Less explored areas of cytopathology in which our particular cytomorphological skills could be used include the field of tumour-circulating cells.[15] This field is growing in the United States and will probably do so in Canada in the near future.

Finally, one long-awaited change that I sincerely hope will become reality in the near future is the recognition of cytopathology as a subspecialty by the Royal College of Physicians and Surgeons of Canada (RCPSC). Although cytopathology has been a well-defined and accepted subspecialty in many countries, including the United States and Australia, for nearly 20 years, Canada still does not have subspecialty certification in cytopathology. With so many changes affecting cytopathology, I think it is crucial to have strong leaders to guide laboratories through these developments, as well as improving quality assurance and continuing education in cytopathology throughout the country.

The field of cytopathology has evolved at a rapid rate since the era of Dr. Papanicolaou, and particularly so in the past 10 years. Not only is cytopathology here to stay – after all, cells are the basis for life and disease – it will expand, especially for non-gynecological specimens. The increasing costs of health care and the pressure for faster diagnosis using ancillary studies on smaller specimens create a very opportune setting for cytopathology.

So, cytopathology is changing and we must keep up with the butterfly coming out of the cocoon so that we do not let it fly away. Let us not forget the words of Alvin Toffler in his book *Future Shock*, published in 1970: "The illiterates of the 21st century will not be the ones who cannot read and write, but those who cannot learn, unlearn and relearn."[16]

Manon Auger
Section Editor, Cytopathology

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La cytopathologie au Canada: Une discipline morphologique en métamorphose

Il faudrait avoir vécu dans un cocon pour ne pas avoir remarque que la discipline de la cytopathologie est en train de changer. Nous savons que les changements sont imminents pour la cytologie gynécologique, résultat de la mise en œuvre au Canada du vaccin contre le papillomavirus humain, sujet qui sera traité dans le prochain numéro de la *Revue canadienne de pathologie (RCP)*. Dans cet éditorial, je veux souligner plusieurs autres changements qui auront un impact sur la cytopathologie.

Les techniques relativement nouvelles des ponctions à l'aiguille fine écho-guidées endobronchiques et des ponctions à l'aiguille fine écho-guidées endoscopiques gagnent en élan.[1–5] Comparées aux ponctions à l'aiguille transtrachéales ou transbronchiques déjà bien établies, obtenues « à l'aveugle » via un bronchoscope flexible qui permet un échantillonnage restreint de larges ganglions lymphatiques sous-carinaires, les ponctions à l'aiguille fine écho-guidées endobronchiques sont plus précises puisqu'elles sont faites sous guidage visuel avec un nouvel endobronchoscope équipé d'une aiguille. Les ponctions à l'aiguille fine écho-guidées endobronchiques rendent des diagnostiques supérieurs comparativement aux techniques traditionnelles (85% versus 66%) et permettent aussi un plus large échantillonnage du médiastin. Les ponctions à l'aiguille fine écho-guidées endobronchiques, conduites par les gastroentérologues durant l'endoscopie, peuvent prélever aussi les ganglions lymphatiques paraœsophagiques et les ganglions lymphatiques médiastinaux inférieurs via l'œsophage; elles sont cependant plus souvent utilisées pour détecter et déterminer les stades des néoplasmes gastro-intestinaux et pancréatiques. Celles qui représentent le plus de défi pour les cytopathologistes sont les lésions kystiques pancréatiques qui nécessitent l'intégration des données de l'imagerie, les données cliniques et biochimiques avec les résultats cytologiques. Tout en échantillonnant un spectre plus large de lésions, ces nouvelles techniques créent aussi un nouvel ensemble de pièges dans l'interprétation dont les pathologistes doivent être conscients.

L'échographie a aussi eu un important impact, dans les dernières années, sur les ponctions à l'aiguille fine thyroïdiennes. Les ponctions à l'aiguille fine thyroïdiennes par palpation directe sont toujours acceptées, cependant un nombre de plus en plus croissant sont conduites sous le guidage de l'échographie, du fait que dernièrement, the American Thyroid Association recommande comme ligne directrice que tous les patients(es) avec des nodules palpables subissent une échographie de la thyroïde.[6,7] Les ponctions à l'aiguille fine écho-guidées thyroïdiennes sont du domaine des radiologistes, cependant un nombre croissant d'endocrinologues et de chirurgiens spécialistes de la tête et du cou les réalisent maintenant parce que la technique est relativement facile à apprendre. Certains cytopathologistes les font aussi maintenant. C'est un domaine avec un potentiel d'expansion pour la pathologie, particulièrement à des endroits dans lesquels la demande en pathologistes est suffisante pour répondre à toutes les demandes exigées d'eux.

Comme pour plusieurs domaines de la pathologie chirurgicale, la cytopathologie a bénéficié de la standard-isation de la terminologie. Suivant le système Bethesda de terminologie pour la cytologie gynécologique, le système Bethesda de terminologie pour la cytopathologie thyroïdienne est maintenant disponible.[8] Ce système évoluera probablement, mais c'est un pas définitif vers la mise en ordre du système chaotique des diagnostics des ponctions à l'aiguille fine thyroïdiennes. Ce système va faciliter la comparaison des données entre institutions et assurer une meilleure compréhension de nos rapports par les cliniciens et une approche plus standardisée du suivi des lésions, en particulier celles qui sont équivoques. Par exemple, une ponction à l'aiguille fine répétée est suggérée pour celles classifiées comme « atypiques de signification indéterminée » parce qu'en majorité, elles sont dues à des peu cellulaires.

L'explosion des diagnostics moléculaires en pathologie n'a pas raté la cytopathologie parce que les spécimens cytologiques sont souvent suffisants et appropriés pour ces examens auxiliaires. Particulièrement, la croissance exponentielle dans l'utilisation de l'hybridation in situ fluorescente dans les spécimens cytologiques (e.g.,

UroVysion pour les échantillons d'urine).[9] Un intérêt croissant a été aussi noté pour l'intégration des données moléculaires pour raffiner les catégories des diagnostics équivoques en regardant de près les translocations chromosomiques, telles *RET/PTC, PAX8/PPARγ*, ou les mutations *BRAF* dans les cas « atypiques de signification indéterminée » dans les ponctions à l'aiguille fine thyroïdiennes.[10]

La normalisation et la validation de l'immunocytochimie dans les prélèvements cytologiques, particulièrement pour les marqueurs prédictifs, deviennent très importantes. La plupart des prélèvements cytologiques sont collectés dans des fixateurs à base d'alcool, contrairement aux prélèvements faits dans des fixateurs en formaline utilisés dans la plupart des procédures des laboratoires immuno-cytochimiques, il devient impératif d'avoir une sélection et une validation de contrôles appropriés.[11] Des directives du groupe d'immunohistochimie du CAP-ACP seraient les bienvenues.

Comme noté dans notre récent éditorial de la *RCP*,[12] l'informatique joue un rôle de plus en plus important en pathologie. L'informatique affecte la cytopathologie de plusieurs manières, par l'imagerie numérique,[13] le balayage complet de lame pour « la télécytologie » diagnostique[14] ou la formation continue, la standardisation des rapports (i.e., l'utilisation de diagnostics « pré-formattes »), et comme un puissant outil d'assurance de qualité dans l'extraction des données et des indicateurs du rendement.

Un domaine moins exploré de la cytopathologie et dans lequel nos compétences cytomorphologiques peuvent être utiles est celui des cellules tumorales.[15] Ce domaine est en croissance aux États-Unis et prendra de l'ampleur au Canada sous peu.

Finalement, un changement tant attendu et que j'espère sincèrement deviendra réalité très bientôt est la reconnaissance de la cytopathologie comme une sur-spécialité par le Collège royal des médecins et chirurgiens du Canada (CRMCC). La cytopathologie est une sur-spécialité bien définie et acceptée dans plusieurs pays, entre autres aux États-Unis et en Australie, depuis près de 20 ans, cependant le Canada est toujours sans certification de la cytopathologie comme sur-spécialité. Avec autant de changements qui affectent la cytopathologie, je pense qu'il est crucial d'avoir des leaders forts qui guident les laboratoires durant ces développements, et aussi pour améliorer l'assurance de qualité et la formation continue en cytopathologie à travers le pays.

Le domaine de la cytopathologie a évolué très rapidement depuis le Dr. Papanicolaou, et plus particulièrement durant les 10 dernières années. Non seulement la cytopathologie est ici pour rester – après tout, les cellules sont bien la base de la vie et des maladies – mais la cytopthologie va s'élargir, spécialement pour les prélèvements non gynécologiques. Les coûts croissants des soins de santé et la pression pour des diagnostics rapides utilisant les examens auxiliaires sur de petits prélèvements créent une bonne opportunité pour la cytopathologie.

Donc, la cytopathologie est en train de changer et nous devons maintenir la cadence du papillon sortant de son cocon pour ne pas le laisser s'échapper. N'oublions pas les mots de Alvin Toffler dans son livre *Future Shock*, publié en 1970: « les analphabètes du 21ème siècle se seront pas ceux qui ne sauront ni lire ni écrire, mais ceux qui ne peuvent apprendre, désapprendre et réapprendre ».[16]

Manon Auger
Éditeur de rubrique, Cytopathologie

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A Case of Vascular Ehlers-Danlos Syndrome Presenting at Autopsy

Sydney Card, BSc, Edward J. Tweedie, MD, FRCPC, and Michael J. Shkrum, MD, FRCPC

ABSTRACT

Ehlers-Danlos syndrome is composed of a group of inherited connective tissue disorders. The vascular type, also known as type IV, is caused by a gene mutation in *COL3A1*, which encodes for type III procollagen. This condition is associated with a shortened lifespan and morbidity due to arterial, gastrointestinal, or uterine rupture. In this article, the case of a previously undiagnosed 36-year-old female who died suddenly from aortic rupture is presented. Laboratory analysis confirmed biochemical and genetic abnormalities.

RÉSUMÉ

Le syndrome de Ehlers-Danlos est composé d'un groupe de dystrophies conjonctives héréditaires. La forme vasculaire, ou syndrome de type IV, est causée par une mutation génétique de *COL3A1*, qui code le procollagène de type III. L'affection se caractérise par une longévité raccourcie et une morbidité due aux ruptures artérielles, gastro-intestinales ou utérines. Dans cet article, nous présentons le cas d'une jeune femme de 36 ans sans diagnostic préalable qui succombe soudainement à une rupture aortique. Les analyses en laboratoire ont confirmé les anomalies biochimiques et génétiques.

Case History

A 36-year-old deceased female had been a patient of a mental health care facility for 2 months. She collapsed suddenly. Despite resuscitative efforts, she was pronounced dead in the local emergency department. An autopsy was performed under a coroner's warrant about 38 hours later. The deceased was noted to have many linear and irregular scars on her face, trunk, and extremities. A scar on the forehead was continuous with a 5 cm long laceration on which Steri-Strips had been applied. Bruises were noted in the right periorbital, sternal, and left femoral areas. Her face was swollen, but there were no dysmorphic features.

During dissection, organs and tissues were noted to be extremely friable, and artefactual tears of the liver, spleen, and descending aorta occurred easily. The cause of death was an acute retroperitoneal hemorrhage, 15 × 15 × 4 cm, originating from an aortic perforation just proximal to the origin of the left iliac artery (Figure 1). At this site, there was a 1 × 0.5 cm intimal defect. Microscopic assessment of this revealed an abrupt loss of intima with transmural rupture (Figure 2). There was a limited dissection plane extending from the defect edges into the tunica media and an associated mixed inflammatory response but no obvious organizing fibroblastic reaction. The rest of the aorta showed

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

minimal fatty streaks and no aneurysms. By microscopy, intimal fibrosis, but no obvious cystic medial degeneration, was observed in additional sections from the distal aorta and iliac arteries. A single, small, healed focus in the aortic wall suggested a previous incomplete tear. Other internal findings included mild to moderate coronary atherosclerosis. There was myxomatous change in the mitral valve. No abnormalities were noted in the gastrointestinal tract. The uterus was absent. In the left femoral area, there was a subcutaneous hematoma (3 × 3.5 × 3 cm) that showed organization.

The marked tissue friability and aortic rupture raised the possibility of Ehlers-Danlos syndrome (EDS). A skin biopsy for fibroblast culture was collected for biochemical and genetic testing (Collagen Diagnostic Laboratory, University of Washington Department of Pathology; www.pathology.washington.edu/clinical/collagen). Results confirmed the diagnosis of vascular-type (type IV) EDS. The amount of type III procollagen was significantly below normal, and the chains also had abnormal electrophoretic mobility. Molecular genetic analysis revealed a point mutation of the *COL3A1* gene (c.2771G>T), which changed the amino acid at position 757 of the triple helix from glycine to valine (Gly757Val).

Discussion

EDS is a group of inherited connective tissue disorders that encompass a wide range of clinical features, notably tissue friability, joint hyper-mobility, and skin hyperextensibility.[1] EDS was formerly subdivided into 10 categories designated by Roman numerals, but classification has been revised on the basis of clinical criteria into six major types: classic (formerly types I and II), hyper-mobility (III), vascular (IV), kyphoscoliosis (VI), arthrochalasia (VII a/b), and dermatosparaxis (VII c).[1] Vascular EDS is a lethal form.[1]

The true prevalence of EDS type IV is unknown due to the rarity of the disease and its under-diagnosis. The estimated prevalence for all EDS cases varies between 1 in 10,000 and 1 in 25,000, with type IV representing approximately 5–10% of cases.[2] EDS type IV is inherited as autosomal dominant, but de novo mutations do arise.[1,2] A gene mutation involving *COL3A1*, situated on the long arm of chromosome 2, affects the production of type III collagen important for the structural integrity of skin, large- and medium-diameter arteries, the gastrointestinal tract, and the uterus.[1,2] Morbidity and mortality arise from rupture of these various structures. Twenty-five percent of patients have one or more major complications by 20 years of age, 80% by 40 years.[3] The median lifespan ranges from 48 to 54 years of age.[3,4] A

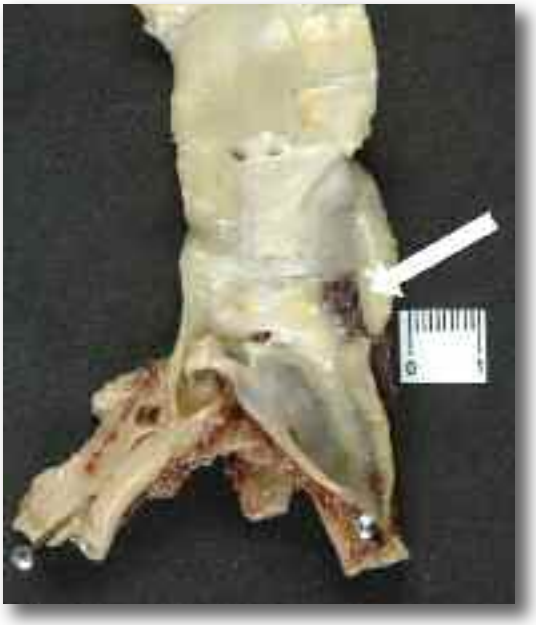

Figure 1. Gross image showing rupture site through a small ulcer in the distal aorta, just proximal to the iliac bifurcation.

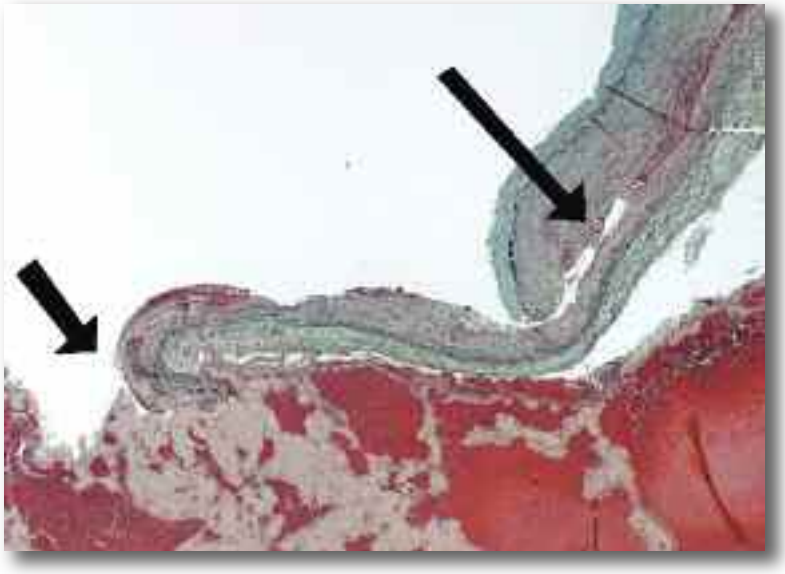

Figure 2. Photomicrograph of the area shown in Figure 1. *Small arrow* shows the edge of the rupture site with peri-aortic hemorrhage. *Large arrow* shows a limited dissection plane extending a short distance from the site of rupture. (Movat pentachrome stain)

diagnosis of vascular type EDS should be considered in any patient 45 years or younger presenting with any of these major complications.[1] Arterial complications are the most common cause of sudden death because rupture is unpredictable and any attempt at surgical repair is difficult due to tissue fragility.[2,3]

A clinical diagnosis of EDS type IV is based on the observation of at least two of four criteria: facial characteristics (thin face with sunken cheeks, bulging eyes, pinched nose, thin lips); thin, translucent skin with visible subcutaneous vessels; easy bruising due to skin and small-vessel fragility, leading to ecchymoses and hematomas; arterial, digestive, and obstetrical complications.[1–3] Uterine rupture can occur, but in this case the clinical basis for hysterectomy was unknown. Skin fragility can lead to a prolonged scarring process.[2] Tissue fragility can be quite marked at autopsy, with tearing of viscera and vessels noted during dissection.[5] The deceased in this case lacked characteristic facial and cutaneous features, but phenotypic expression is variable and subtle.[2,4] The deceased did have an organizing soft tissue hematoma in the left femoral area, which appeared to antedate the aortic rupture site. Few patients who present with arterial complications report previous trauma.[4]

Light microscopy of the aorta in EDS type IV is non-diagnostic.[4] Hemostasis tests are generally normal.[2] When vascular EDS is suspected, confirmation is determined by laboratory analysis. Tests currently available include biochemical assays for type III procollagen and molecular genetic analysis of the *COL3A1* gene.[1–3] Diagnosis can be made post-mortem.[5] Both tests can be done by culturing skin fibroblasts and are performed in specialized laboratories due to the rarity of the disorder.[5] In this case, there was biochemical and molecular genetic confirmation of the disease. Sampling of aortic tissue for molecular testing is a common misconception; however, alternative post-mortem sources for deoxyribonucleic acid include frozen blood or tissue (e.g., liver or spleen).[6]

In conclusion, EDS type IV can present as a sudden unexpected death requiring an autopsy.[3,5] Tissue fragility and rupture of any major vessel, the uterus, or the gastrointestinal tract are clues.[5] A suspicion of EDS type IV at post-mortem can be confirmed using cultured fibroblasts by a biochemical assay showing type III collagen secretion abnormalities, and molecular genetic studies identifying a *COL3A1* mutation.[5] Genetic counselling of living relatives must be advised.[5]

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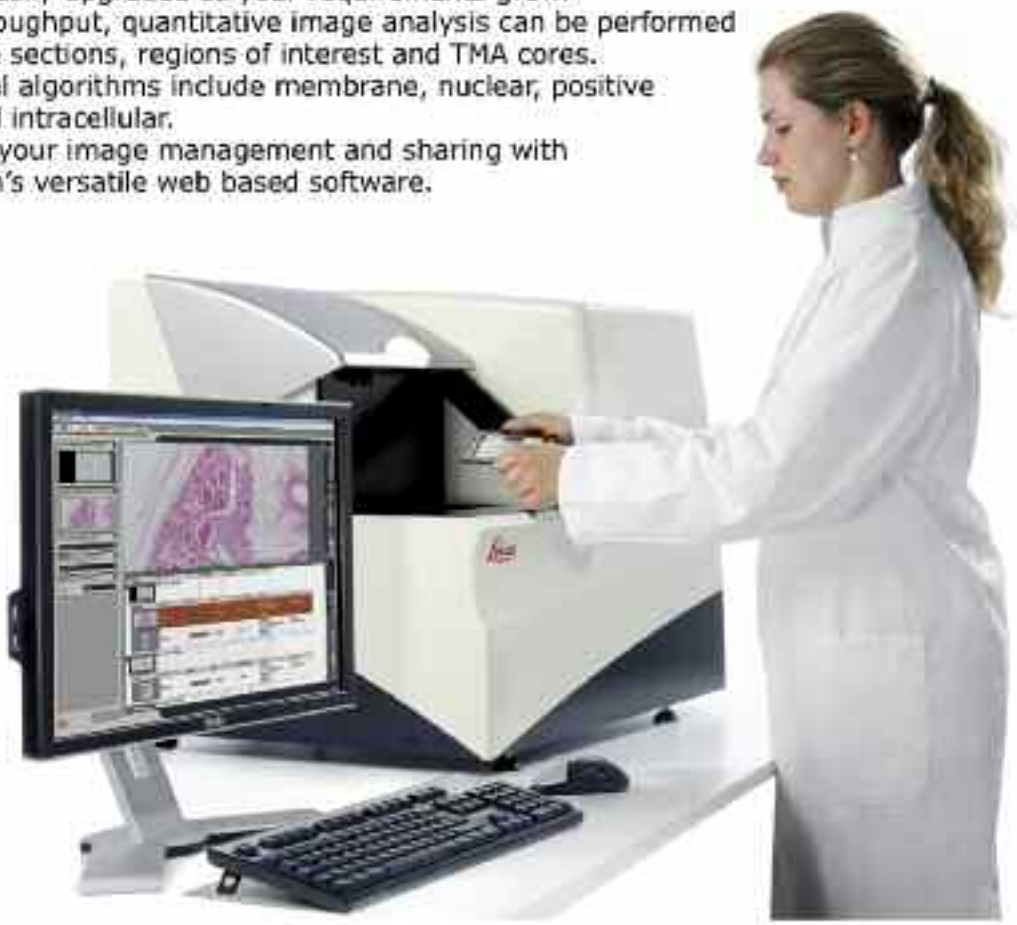

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The Origin of Basic Science Pathology: An Unrecognized Event in the Medical History Literature

Guillermo Quinonez, MD, MS, MA, FRCPC

ABSTRACT

The history of pathology is commonly written under the definitional notion of pathology as the "science of disease." Without denying that *pathology* means "the study of disease," such an approach makes it difficult to discriminate between the history of pathology as a basic science and as a clinical science. Using the history of a concept as an approach, a systematic review of the classic textbooks in pathology written between the years 1500 and 1800 reveals that anatomical pathology began as the result of the development of the concept of "solidism" (organ theory) and the scientific knowledge it determined. This approach demonstrates that the history of pathology allows for the recognition of a shift in the literature from signs and symptoms to the morphological evidence of disease. This previously ignored event signalled the beginning of basic science pathology and therefore provides historical information that does not replace but, rather, complements that obtained using the notion of pathology as the science of disease.

RÉSUMÉ

L'histoire de la pathologie s'écrit généralement dans les limites de la définition de la pathologie comme étant la « science qui a pour objet l'étude des maladies ». Sans rejeter cette définition, notons que cette approche tend à confondre l'histoire de la pathologie en tant que science fondamentale et celle de la pathologie en tant que science clinique. L'historique d'un concept constituant la méthode d'analyse, une étude systématique des manuels de pathologie classiques écrits dans la période allant des années 1500 aux années 1800 révèle que l'anatomopathologie est née du concept de « solidisme » (théorie de l'organe) et de la connaissance scientifique qu'il déterminait. Cette méthode démontre que l'histoire de la pathologie permet de retracer le changement de paradigme qui passe des signes et des symptômes aux manifestations morphologiques de la maladie. Cet évènement passé inaperçu jusque-là donne le coup d'envoi à la science fondamentale de la pathologie et offre par conséquent de l'information historique qui ne remplace pas celle obtenue en utilisant la notion de pathologie comme la science de la maladie, mais qui y est plutôt complémentaire.

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Pathology, as a morphological science, has a long history that has developed under several modalities of thinking. The initial modality was the extension of the study of normal anatomy known as anatomical pathology or morbid anatomy.[1] Through this modality evolved the concept of "solidism," that is, the idea that disease is manifested primarily in body organs. In the first half of the 19th century, solidism was enriched by the concepts of tissue and cell theories, becoming the basis on which pathology transformed into a modern medical discipline.

The history of the inception of modern pathology has been written in various ways,[2] but it has always been influenced by the definition of *pathology* as "the study of disease."[3–5] This approach unquestionably offers important information; however, it does not discriminate between pathology as a clinical science (clinical knowledge generated by natural experiments) and pathology as a basic science (knowledge about the reactions of the body to injury generated by natural and man-made experiments). The latter is now structured as "cellular responses to injury," "inflammation," "tissue repair," "hemodynamic disorders," and "neoplasia."[6] The definition of pathology as the study of disease focuses on the socio-economic-cultural aspects of the specialty and describes the history of the beginnings of pathology as a clinical science only.

Historiographically, one could argue that the history of solidism is a foundation on which the beginnings of anatomical pathology as an independent science can be explained. This approach would make clear the distinction of the beginnings of anatomical pathology as a clinical science and of anatomical pathology as a basic science. The present essay demonstrates that the scientific knowledge determined through solidism was the key reason for the origin of anatomical pathology as a clinical science. A shift in focus in the investigation of disease from signs and symptoms to the nature of the underlying organic lesions per se under the same concept would create the conditions for the origin of anatomical pathology as a basic science. These closely related events are recognized in the traditional primary sources when re-analyzed using this approach.

The Beginnings of Anatomical Pathology as a Clinical Science through Solidism

During the Renaissance period, the interpretation of morphological findings when performing autopsies was so closely associated with the humoral theory of disease that it was impossible to evaluate them independently. Although a focus on organs to explain the cause of death was evident among those anatomists/clinicians who were performing autopsies at hospitals, solidism was only a small conceptual shift from humoralism. Physicians were not ready to accept a new paradigm of disease[7] as humoralism satisfactorily explained signs and symptoms and prognosis and offered convenient arguments for management procedures.[8]

Esmond Long, in his book on the history of pathology, links the limited implications of the knowledge generated by the autopsy at that time with the foundation of the science of pathology. He does this in his comments regarding Antonio Benivieni (1443–1502), the physician considered to be the pioneer anatomical pathologist.[3] These limitations can be summarized as follows. First, observations alone did not constitute a knowledge base for founding a new science; they needed a framework. One can conclude that he was referring to the lack of development of a concept (solidism). Second, the humoral theory of disease continued as the only idea under which anatomical findings were interpreted. Third, new observations were isolated efforts that did not have any significance on present and future generations of physicians. Fourth, no systematization of the knowledge was attempted. And, finally, there was an absence of a scientific method.[9] In short, post-mortem investigations were isolated exercises directed to find simplistic answers that explained the cause of death and were interpreted under the traditional, general idea of humoralism.

Benivieni's *De Abditis Nonnullis Ac Mirandis Morborum et Sanationum Causis* (On Some Hidden and Remarkable Causes of Disease and Recovery), published in 1507, provides an example of this simplistic approach.[10] A product of the Renaissance, the historical literature accepts this as the first medical text that formally included autopsy findings. His focus was primarily clinical, not anatomical. However, solidism is clear in the text, which consists of 111 short clinical histories together with 13 cases including brief anatomical observations of body organs aimed at explaining the apparent cause of death. Two cases contain descriptions of two autopsies for a total of 15 sets of observations derived from 13 cases. The interpretation of these anatomical findings is made using the humoral theory of disease (e.g.,

Case XXXIII) and the ideas of Galen (e.g., Case LXI). There is neither organization nor systematization of knowledge as cases are described in no particular order and post-mortem descriptions are reduced to one small paragraph. The impact of this book on future generations was limited because its importance was not fully appreciated. Knowledge generation lacked scientific methodology since none had yet been described. However, empirical observations were considered scientific in the 16th century.

Benivieni's contribution already represents solidism from the perspective of understanding signs and symptoms of disease. Although he continues to receive recognition for this limited approach, his efforts were not made in isolation. The historical literature mentions other authors who made similar contributions during the Renaissance period. For instance, Garrison, in his classic work on the history of medicine, mentions Jean Fernel (1506–1588) and Guillaume de Baillou (1538–1616).[11] Similarly, Carlino, in his well-documented book on the history of anatomy, lists several other physicians/anatomists, such as Realdo Colombo (1516–1559), Bartolomeo Eustachio (1514–1574), Jacopo Berengario da Carpi (1460–1530), and Niccolo Massa (1485–1569). All of these individuals published medical textbooks that included post-mortem examinations.[7]

The limited implications, described by Long, of the knowledge generated by the autopsy to pathology during the Renaissance were unchallenged in the 17th century. There was one exception, however, in Theophilus Bonetus (1620–1689), who wrote *Sepulchretum sive Anatomia Practica*, a collection of 3,000 protocols from post-mortems during the 16th and 17th centuries that was published in 1679. The report contains descriptions of autopsies performed by famous anatomists such as Glisson, Willis, Vesalius, Fallopius, Fabricius, Fernel, Harvey, Brunner, and the Bartholins, among others. This work was republished, corrected, and augmented by Jo. Jacobus Mangetus in 1700. According to subsequent writers, both versions were full of errors.

In the 18th century, the limitations described by Long began to be overcome. For the first time, a database was created where morbid anatomical observations were systematized correctly using clinico-pathological correlations. This contribution is attributed to Giovanni Battista Morgagni (1682–1771), who wrote *De Sedibus et Causis Morborum per Anatomen Indagatis* (*The Seats and Causes of Disease Investigated by Anatomy*) in 1761.[12] The text is written in the form of letters characterized by respect and admiration. Its focus is on disease in general with an emphasis on solidism using observation and analogy, as well as the application of a scientific methodology.[12] It is clear that the author's intention was to collect all information available in the literature about the practice of medicine since the time of the Greeks up to the middle of the 18th century. In reality, the book is a textbook of general medicine that describes disease from the points of view of cause, public health, pathogenesis, signs and clinical symptoms, differential diagnosis, pathology, prognosis, and treatment.

Seats and Causes of Disease was written with the intention to correct and expand *Sepulchretum*. Morgagni's criticism of the latter volume is made strong and clear in the preface and at the beginning of each letter. The letters are collected in five books consisting of the cases published in *Sepulchretum*, others contributed by the author and by his teacher Valsalva (1666–1723), cases related to him by others either verbally or by letters, those collected from the literature, and cases published by academies that honoured the author with a membership. There are also frequent references to Hippocrates, Galen, and other ancient authors, including Benivieni.[12] The book calls specific attention to the use of the autopsy in clinical practice.

Anatomical pathology is an important component of the book.[12] There is emphasis on the lesions of organs, using the findings to make clinico-pathological correlations. That is, it incorporates anatomical descriptions with the intent of explaining clinical cases. The emphasis is so strongly clinical that the author even discusses specific disease entities in some detail, such as hydrophobia, its cause, and treatment. Some letters contain only brief references to autopsies or none at all. Yet Morgagni strongly defends the autopsy against its critics. Descriptions are clinically, not pathologically, orientated.

In summary, *Seats and Causes of Disease* embodies the beginnings of modern clinical medicine and of pathology as a clinical science. However, it does not represent the organization and structure of knowledge that will characterize the literature in anatomical pathology as a basic science. The latter is the essence of the discipline. The organization of the material is that of a curious clinician

trying to understand the nature of disease. Nevertheless, an explanation of signs and symptoms based on the gross morphological findings of organs at autopsy typifies a new systematized approach to the study of disease as a biological entity based on observation as a method and on solidism as a concept, that is, anatomical pathology. Surgeon-anatomists such as Pott, the Monros, and the Meckels moved this form of writing forward.

The Beginnings of Anatomical Pathology as a Basic Science through Solidism

Morgagni and the surgeon-anatomists dealt with clinical and pathological information as clinicians, not as pathologists. Their "anatomoclinic" approach was later perfected at the Paris School of Medicine.[1] In contrast, pathologists organize and systematize anatomical information based on pathological findings first and then correlate it with signs and symptoms. The distinction is important and must be emphasized.[4] Pathologists' source of data is morphology and not the information given by patients or derived from clinical presentations. As a result, the reaction of tissues to injury forms the core knowledge of the discipline. The anatomoclinic approach only uses the information provided by this knowledge to make clinico-pathological correlations; its primary objective is not to study it and explain it. This is the pathologist's role.

Matthew Baillie (1761–1823) in the last decade of the 18th century offered a different approach from Morgagni's for the organization and systematization of anatomical knowledge in pathology. Baillie organized and structured knowledge under the concept of solidism based on pathological findings rather than clinical presentations. The approach was the result of Baillie's personal experiences with dissection, his reading of the literature, and the influence of John Hunter. Baillie was so close to Hunter that he was either inspired or directed to this approach by him. Since 1762, Hunter had been writing on topics relevant to basic pathology. In one of the four books that he wrote, he focused his attention on inflammation and wound healing, among other topics, indicating that the reaction of body organs to injury was within his purview.[13] It is possible that this approach was taught to Baillie or that Hunter simply called his attention to it. In addition, Hunter provided Baillie with free access to his museum.[14] The creation of such museums challenged knowledge obtained from classic texts and represented a new way of producing knowledge based on careful observation of collected pathological specimens. The content of Hunter's museum, as used by Baillie, re-emphasized the new focus of observation for explaining disease. This information would have influenced Baillie's approach to the study of disease.

In his work *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*, published in 1793,[15] Baillie introduced an organization and systematization of knowledge around solidism that became standard in the new medical discipline of pathology. New observations were no longer made in isolation; they became a knowledge base for the foundation of pathology as a basic science. The information was not written in epistolary style, and slowly adopted the written format of anatomical pathology seen in the 19th century.[16] By then, humoralism was not the prevalent explanation of disease and had been replaced by mechanism and vitalism as the dominant general ideas. Similarly, the scientific method was beginning to make an impact on medicine. The new approach led to the production of the core knowledge of anatomical pathology, that is, the reaction of the body to injury. At the end of the 18th century, and distinct from Renaissance times, what mattered was the systematic observation of morphological findings at autopsy, and not authority.[17]

A statement by Baillie in the preface of *The Morbid Anatomy* is a "manifesto" that set the basis on which to develop pathology as a discipline through the knowledge generated by solidism. By contrasting his contribution with that of Morgagni, he set the stage for the new approach.[15] The organization and content of *The Morbid Anatomy* was seminal to the future of pathology and subsequently characterized the literature in the field as a basic science. This new format allowed for the organization of data by anatomical site, particularly by organ, similar to that found in modern textbooks of pathology. In other words, the content reflected anatomical findings (i.e., lesions) observed with the naked eye and compared with normal organs. The basic gross morphological reactions of organs to injury formed the nucleus of the text and were described in each organ of the human body. This was followed at the end of each chapter by a short description of symptoms, where they were explained briefly using anatomical findings; that is,

after all, the goal of pathology. In the text, there were hypothetical functional explanations based on anatomical findings. The possible role of functional disturbances when there are no obvious pathological lesions was also raised.

The Beginnings of the Medical Specialty of Pathology: A Reassessment

A concept – solidism – relevant to the beginnings of pathology as a clinical and basic science is recognized in these historical events. This analysis indicates that this concept was evolving with the performance of hospital autopsies following the Renaissance period. Solidism became a framework on which the biology of disease could be understood and resulted in the consideration of body organs as the primary sites of disease. (Solidism could also be named "organ theory" because the focus of observation was body organs.) The concept of organ systems did not exist at that time, and the microscope had not yet been introduced into pathology. The fundamental element for understanding such biology was therefore the macroscopic morphological lesions demonstrated in the organs at the autopsy, that is, the reaction of organs to injury (the core knowledge).

No one individual created the *concept* of solidism. If it is possible to identify particular proponents, it is because of the focus of the historical literature on the texts that have survived over time. For instance, when Benivieni's book was published by his brother, there were several other texts about the same topic. Bonetus collected only the experience of the previous two centuries.[10,12] Morgagni was more inclusive, but followed the ideas of Bonetus. Baillie represented the approach developed by his teacher, Hunter.

The *knowledge* generated by solidism was also not created by one individual. *The Seats and Causes of Disease* and *The Morbid Anatomy* sometimes offered information that was not completely new, as illustrated by the bibliographic references contained in both books. This was also true of information provided by secondary sources.[12,14,15] In these works, there were examples of experimentation and discussion of basic reactions of tissues to injury since antiquity. Yet the originality in these two treatises was expressed in the organization and structure of knowledge through the concept of solidism.

Solidism determined anatomical knowledge that was used in interpretations of pathology as a clinical as well as a basic science. The first, pathology as a clinical science, was known as the anatomoclinic interpretation and consisted of the correlation of signs and symptoms with anatomical findings. It corresponded to Morgagni's contribution and was known in the literature as the "localistic organic interpretation" of the seats of disease.[1] Clinical pathology then evolved as the study of the particular morphological manifestations of disease using natural experiments. This knowledge would partially, albeit importantly, contribute to the understanding of the biology of disease. The Paris School of Medicine advanced it in the first quarter of the 19th century and helped to introduce a modern conception of disease.

The second, pathology as a basic science, was the interpretation used by pathologists and consisted of the correlation of anatomical findings with signs and symptoms. This was Baillie's contribution. Basic science pathology evolved more slowly as the study of the general morphological manifestations of disease. This knowledge supported clinical pathology and was the contribution of the German School in the first half of the 19th century.[18] Participation of the New Vienna School, with Carl Rokitansky, in the second quarter of the 19th century was also significant.[19]

The historical approach based on the definition of pathology has contributed to a lack of distinction between the history of pathology as a clinical and basic science. While it is true that the contributions of Morgagni and Baillie have been recognized in the literature, the implications of their work have not been acknowledged.[11,14,20] There is no recognition in the literature that the first deals with clinical science and the second with basic science pathology.

In conclusion, a historical approach under the definition of pathology as "the study of disease" describes both the beginnings of clinical pathology and also those of an anatomical conception of disease. The line taken in this article, however, elucidates the distinction between the origins of clinical and basic pathology. Both approaches are needed when studying the history of this discipline since they are complementary. It has been my intention to underscore the importance of an analysis of the history of pathology with added critical elements obtained under pathology as "the science of disease." Nonetheless, a

comprehensive assessment of the impact of this approach in an analysis *a posteriori* should not be independent of the history of other concepts (e.g., tissue and cell theory), other scientific disciplines (e.g., physiology, bacteriology), technological advances (e.g., microscopy), and socio-cultural contexts. As demonstrated by Rosen in 1944, the origin of a medical specialty is a multi-factorial process.[21] Therefore, a complete analysis of the history of pathology will require a combination of both approaches to maximize our understanding.

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Rising Incidence of Syphilis Infection in Canada: A Case Report of Syphilitic Placentitis

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ABSTRACT

The Public Health Agency of Canada reports an increasing incidence of syphilis in the general population throughout Canada; as a corollary, the rate of congenital syphilis cases is on the rise as well. In 2006, 1,311 cases of adult syphilis were detected and the overall rate increased by 900% when compared with 1997.

We present a case of syphilitic placentitis to alert pathologists and clinicians to the increasing possibility of encountering syphilis in modern practice. A patient with minimal antenatal care presented late in this pregnancy. She had been diagnosed with syphilis 3 years previously and treated with doxycycline because of a penicillin allergy. At presentation to the hospital, syphilis serology was positive. The neonate's serology was positive for syphilis antibodies; however, there were no signs of congenital syphilis. The placenta was found to have histiocyte-predominant villitis and stem villi sclerosis. The presence of *Treponema pallidum* within the chorionic plate was demonstrated by the Steiner silver stain. This case shows that routine screening for syphilis remains a justified standard of antenatal care, and pathologists must consider the possibility of syphilis when encountering histiocyte-predominant villitis and plasma cell villitis with placental endovasculopathy.

RÉSUMÉ

L'Agence de la santé publique du Canada rapporte une augmentation de l'incidence de la syphilis dans la population en général partout au Canada; il s'ensuit que le taux de syphilis congénitale est aussi en hausse. En 2006, on dénombre 1 311 cas de syphilis chez les adultes et le taux en général a augmenté de 900 % comparativement à 1997.

Nous présentons un cas de placentite syphilitique pour alerter les pathologistes et les cliniciens à la possibilité croissante d'avoir à diagnostiquer la syphilis en cabinet. Une femme enceinte n'ayant pas bénéficié de soins prénataux pour ainsi dire consulte en fin de grossesse. Elle a eu la syphilis trois ans auparavant pour laquelle elle a été traitée à la doxycycline en raison de son allergie à la pénicilline. À l'hôpital, la sérologie révèle la présence de la syphilis chez la mère et d'anticorps chez le nouveau-né, qui ne présente pas toutefois de signes de syphilis congénitale. L'analyse histologique du placenta met en relief une inflammation des villosités choriales où prédominent les histiocytes ainsi qu'une sclérose du tronc villifère. La présence de *Treponema pallidum* dans la plaque choriale a été démontrée par la coloration à l'argent selon la méthode de Steiner. Ce cas illustre que le dépistage courant de la syphilis reste une norme de soin prénatal justifiée, et les pathologistes doivent considérer la possibilité de syphilis à la constatation d'une inflammation des villosités à prédominance d'histiocytes ou d'une inflammation des villosités où abondent les plasmocytes, accompagnée d'une angiopathie placentaire.

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Syphilis is caused by the spirochete *Treponema pallidum*; modes of transmission include sexual, transplacental, and blood-borne.[1] Congenital syphilis is defined as syphilitic infection present in utero and at birth. The majority of infants are infected in utero and the risk of transmission in untreated women is 70–100% with primary or secondary syphilis, 40% with early latent syphilis, and 10% in late latent stages.[2] Fetal demise occurs in 40% of pregnancies.[3] The diagnosis of congenital syphilis is based on positive serology accompanied by clinical manifestations. While Venereal Disease Research Laboratory (VDRL) positivity in cerebrospinal fluid (CSF) indicates congenital neurosyphilis, positive reaction in the fetal blood may be due to maternal antibodies, which can remain in the maternal circulation for up to 12 months. Early clinical manifestations of congenital syphilis include fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, and neurosyphilis; however, some patients may be asymptomatic. Late manifestations can include interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, anemia, Hutchinson's teeth, and neurosyphilis.[1] The standard treatment is penicillin, which is administered to the newborn even if the mother has been treated during the pregnancy since the risks of treatment are negligible.

Case Report

A teenage mother arrived in triage with irregular contractions. She was determined to be of approximately 39 weeks' gestation and had had no antenatal care. Ultrasound examination revealed a 5.78 cm thick placenta with normal fetal anatomy. Serology was positive for VDRL. The public health laboratory was contacted, and the patient was found to have a record of positive syphilis serology with a titre of 1:128 approximately 3 years earlier. At that time, the patient had been treated with a 3-week course of doxycycline because of allergy to penicillin. Her current titre was 1:64 indicating that either reinfection or treatment failure had occurred. A lumbar puncture showed that the patient had no neurosyphilis as CSF was non-reactive for VDRL and fluorescent treponemal antibody absorbed (FTA-ABS). At that time, the membranes were intact and testing for group B streptococci was negative.

The patient left against medical advice and returned in labour 2 days later. She had a spontaneous vaginal delivery and was afebrile during the delivery. The infant weighed 3,138 g and had no external physical signs of congenital syphilis. The neonate was found to have positive syphilis serology (immunoglobulins G and M), syphilis reagin quantitative titre 1:32, and reactive syphilis *T. pallidum* particle agglutination (TP-PA) but negative results in CSF and normal long bone radiographs. These results in the neonate were felt to be consistent with either an asymptomatic infection or the presence of maternal antibodies in the neonatal blood. The baby received a 14-day course of penicillin and, on subsequent visits, revealed no stigmata of congenital syphilis. The mother stated she was allergic to penicillin and left against medical advice. She has been lost to follow-up.

Pathological Features of the Placenta

Gross pathological examination of the placenta showed a significantly enlarged placenta weighing 619 g (above 90th

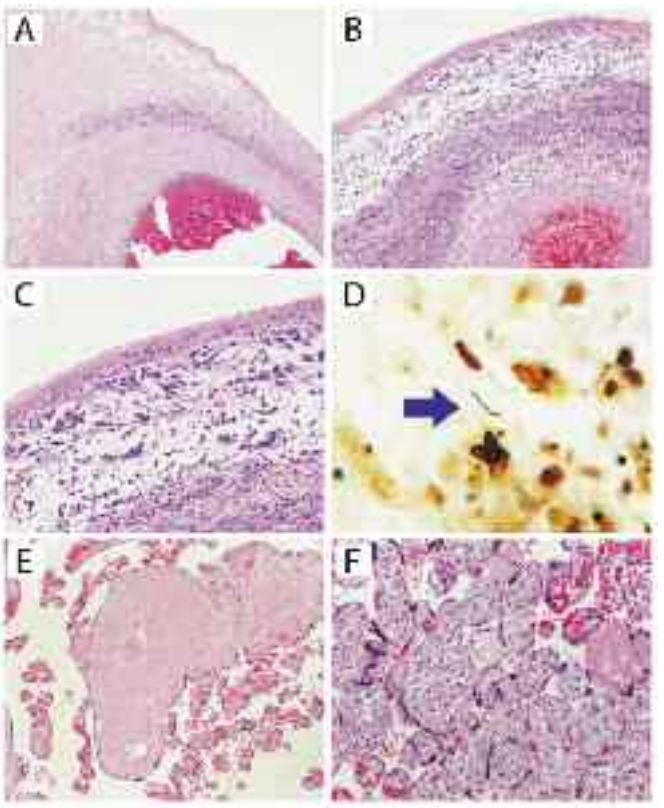

Figure 1. Perivasculitis within the cord (*A*). A band of subacute inflammation in the superficial chorionic plate (*B* and *C*) with *Treponema pallidum* (*D*). Sclerosis of stem villi (*E*). Histiocyte-predominant villitis (*F*). (*A, B, C, E*, and *F*, hematoxylin and eosin; *D*, Steiner silver stain).

percentile for 39 weeks' gestation; 10–90th percentile reference range 426–611 g) with a dull appearance to the membranes. No focal lesions were seen. Microscopically, the membranes revealed subacute chorioamnionitis with a mixed mononuclear-neutrophilic infiltrate in the membranes and in the superficial chorionic plate (Figure 1). There was perivasculitis within the chorionic plate and the cord, where the perivascular inflammatory cells were migrating to the Wharton's jelly with focal degeneration of the tissue; no concentric necrosis was seen. The placental disc showed areas of villi expanded by collections of CD68-positive histiocytes (histiocyte-predominant villitis) and focal concentric vascular sclerosis within the stem villi. Appreciable numbers of plasma cells within the villi or the chorionic plate were not seen with hematoxylin and eosin or by immunohistochemistry for CD38. Immunohistochemical staining for cytomegalovirus (CMV) was negative. A Steiner silver stain revealed spirochetes with corkscrew morphology within the band of subacute inflammation of the superficial chorionic plate, focally up to three per ×40 high-power field.

Discussion

After nearly two decades of decreasing trends in the number and rate of reported cases, syphilis was thought to be on the verge of elimination from Canada. However, both the rate and number of cases have increased over the past several years, within both sexes and throughout all age groups. This includes a rise in congenital syphilis.[1,4] According to the Public Health Agency of Canada, the rate of syphilitic infection in Canada attained a low plateau of 0.4 per 100,000 in 1996–1997; however, since then the rate has been steadily increasing (Figure 2).[1] The highest rates (per 100,000 in 2007) were in British Columbia (7.7), Alberta (6.5), Quebec (4.8), and Ontario (2.8). The rates increased in both males and females, but more so in males (6.2 in males and 0.9 in females per 100,000 in 2007), which has been partially attributed to outbreaks in men who have sex with men. Among the possible causes of the overall increase in syphilis incidence are "condom fatigue" and reduced fears of acquired immunodeficiency syndrome due to the improved treatment of human immunodeficiency virus infection. The rate of congenital syphilis has also been increasing, which probably reflects the overall higher prevalence of the infection.

Pathological findings in the placenta, similar to other TORCH (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) infections, represent a range

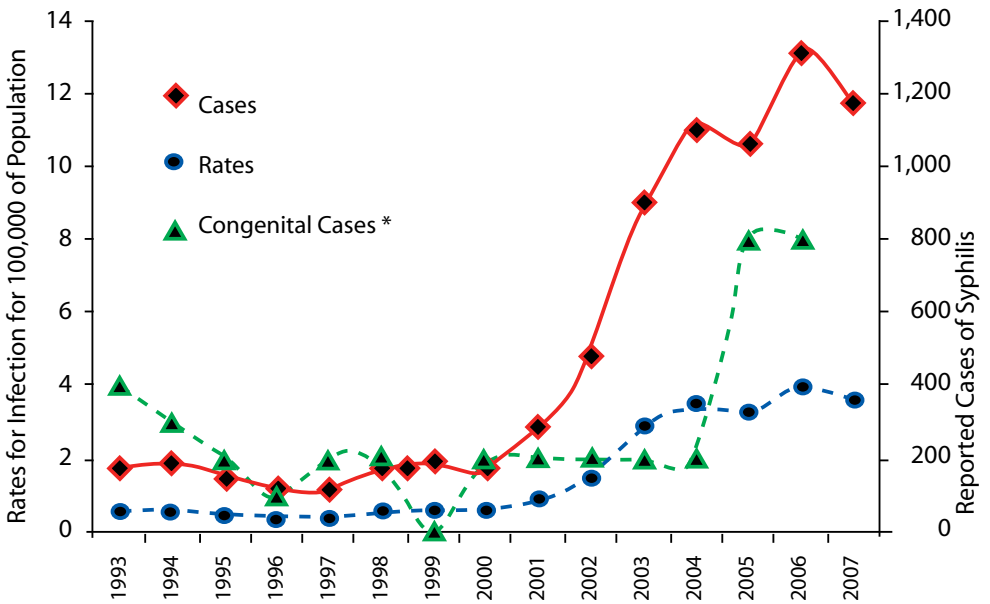

Figure 2. Reported cases of syphilis (*red*) in Canada from 1993 to 2007, with rates of infection (*blue*) and congenital syphilis (*green*) from 1993 to 2007. Rates are per 100,000 of population. *No data available for 2007.

of inflammatory changes. Grossly, the placenta can have two distinct patterns when infected with syphilis. In one scenario, histiocyte-predominant villitis leads to increased placental weight and a pale appearance. The second pattern is fibrosclerosing villitis, in which the placenta is small and firm, with villous mineralization and fibrosis. Microscopically, the most common features of syphilis are an endothelial and fibroblastic proliferation and chronic villitis with a prominent mononuclear infiltrate containing plasma cells. A plasma cell infiltrate may often also be present in the decidua with associated necrosis. Another finding may be perivascular fibroblastic proliferation in villous stem vessels.

The most important differential diagnosis is CMV infection. The absence of CMV inclusions and lack of staining for CMV antigens by immunoperoxidase should prompt consideration of syphilis. Other less specific features include villous immaturity with an increase in Hofbauer cells (histiocyte-predominant villitis); concentric mural vascular sclerosis with perivasculitis (proliferative endovasculitis); and necrotizing umbilical periphlebitis, which consists of necrotic cell debris and an eosinophilic precipitate found around umbilical veins. Necrotizing funisitis was described as a classic finding of syphilitic infection but was later felt to be non-specific. Many other organisms, such as streptococci and *Candida*, can be associated with necrotizing funisitis. Demonstration of spirochetes by silver stains, including Warthin-Starry, Steiner, and Dieterle, is best accomplished in the umbilical cord.[5–7]

Our case demonstrated some of the features of syphilitic infection, including an enlarged placenta, histiocyte-predominant villitis, focal concentric vascular sclerosis within the stem villi, and perivasculitis within the cord and the superficial chorionic plate. The placenta showed significant subacute chorioamnionitis, which may be seen in syphilis but is not a classic feature. A prolonged length of time between spontaneous rupture of membranes and delivery is a major risk factor for chorioamnionitis and may have accounted for this. However, the clinical record does not show clear risk factors for other infections immediately before delivery: the patient in this case presented with intact membranes 2 days before labour, was negative for group B streptococci, and was afebrile during the labour.

This case is a reminder that syphilis can be encountered in present-day practice. Pathologists need to be familiar with its presentations and morphological findings. In this case, the diagnosis was first established serologically; the pathologist was alerted to this and therefore looked for specific features within the placenta. In many instances, however, an unexpected case of syphilis may be encountered and, since the findings are relatively non-specific, syphilis may not be foremost in the differential diagnosis. Clinically, routine screening for syphilis remains justified as a standard of care for all pregnant women, and it is recommended that all high-risk patients be re-screened later in pregnancy or after delivery.

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Pathology Education in Canada: Results of a National Survey

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ABSTRACT

Purpose: Pathology is a key component of medical education, but there is little known about how pathology is taught to Canadian medical students. Improving pathology education, which may improve the recruitment of medical students into pathology residencies, requires that we have a better understanding of how curricular changes have affected pathology teaching in Canada.

Methods: We surveyed pathology educators across Canada, using a quantitative and qualitative survey instrument, to assess five educational areas: preclinical medical education in pathology, pathology electives, pathology as a career choice, student feedback about pathology teaching, and overall features of pathology education.

Results: We found that pathology has relatively limited teaching hours at most medical schools and that interactive small-group teaching was replacing didactic lectures. Pathologists use gross photographs and photomicrographs rather than actual pathological specimens or autopsies to teach medical students. There is limited exposure to pathology as a career. Pathology teaching focuses on pathogenesis rather than diagnostic pathology, and students are not expected to learn histopathological interpretation.

Conclusions: Canadian pathology educators believe that medical students do not learn enough about pathology; but despite this limitation, it is clear that Canadian medical students rate their pathology teaching very highly.

RÉSUMÉ

Objectif : La pathologie est une composante clé de la formation médicale, mais on en sait peu sur l'enseignement de la pathologie aux étudiants en médecine canadiens. L'amélioration de la formation en pathologie, susceptible de faciliter le recrutement d'étudiants en médecine dans les programmes de résidence en pathologie, n'est possible que si nous connaissons mieux le retentissement de l'évolution du programme d'études sur l'enseignement de la pathologie au Canada.

Méthode : Nous avons interrogé les enseignants de pathologie du Canada dans le cadre d'un sondage comportant des volets quantitatif et qualitatif pour évaluer cinq domaines de la

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formation : la formation médicale préclinique en pathologie, les stages en pathologie, la pathologie comme choix de carrière, la rétroaction des étudiants en médecine à propos de l'enseignement de la pathologie et les caractéristiques générales de la formation en pathologie.
Résultats : Dans la plupart des facultés de médecine, peu d'heures sont consacrées à l'enseignement de la pathologie et l'enseignement interactif en petits groupes remplace peu à peu les cours magistraux didactiques. L'enseignement est illustré par des clichés de macrophotographie ou de microphotographie, non pas par de réels prélèvements ou par des autopsies. La présentation de la pathologie comme choix de carrière est limitée. L'enseignement de la pathologie se concentre sur la pathogenèse plutôt que sur la pathologie diagnostique, et l'interprétation histopathologique ne constitue pas une exigence de la formation.
Conclusion : Les enseignants de pathologie canadiens déplorent que les étudiants en médecine n'apprennent pas suffisamment la pathologie; malgré cela, les étudiants en médecine canadiens ont l'enseignement de la pathologie en très haute estime.

Medical education in Canada has undergone substantial changes over the past 20 years. At many schools, integrated themes or blocks have replaced individual courses.[1,2] Didactic teaching has been replaced by problem-based learning.[3] Some schools have also begun teaching large numbers of students across geographically separate distributed campuses.[4]

Pathology education for Canadian medical students has been deeply affected by these changes. Pathology is (or ought to be) central to the preclinical education of all future physicians,[2,5–7] even though the overwhelming majority of medical students will not become pathologists. Recent publications from both the Association of Faculties of Medicine of Canada[8] and the Association of American Medical Colleges[9] have demonstrated a renewed interest in promoting basic science education in medical school, as part of high-quality generalist training. In addition, pathology education is important for the recruitment of medical students into pathology residency programs[6]: too few Canadian medical students elect to become pathologists,[10] a problem that has attracted the attention of not only the Canadian Association of Pathologists[11] but also a recent high-profile provincial public inquiry into pathology practice.[12]

Several surveys of pathology education have been conducted in the United States and the United Kingdom to identify trends in pathology teaching time or teaching approaches,[1,13] or to find links between teaching styles and pathology marks on medical student examinations.[14] A recent survey of pathology educators in the United States[15] found interesting educational disparities: for example, in approximately half of the surveyed schools pathology is taught as a separate discipline or course, while in the remaining schools pathology is incorporated into integrated blocks. No similar analysis has been published regarding Canadian medical education in pathology. A brief survey was therefore created to solicit this information from every medical school in Canada.

Methods

A telephone and e-mail survey was designed to identify key features of pathology education across Canada. Some of the survey questions were modelled on a previously published survey from the United States,[15] after permission was received from its author (Dr. C.R. Taylor).

There are 17 accredited medical schools in Canada, of which 13 use instruction in English, one is bilingual, and three use instruction in French. Pathology course or theme directors, or experienced pathology teachers, were identified from all 17 schools. Following the receipt of institutional ethical approval, these educators were contacted by telephone or e-mail and asked to complete the survey. Responses were received from 16 of the 17 schools (response rate 94%) and consent to participate was received from every respondent. The survey consisted of 27 questions, exploring each school's approach in five areas:

1. Preclinical education in pathology
2. Pathology electives
3. Pathology as a career choice
4. Student feedback about pathology teaching
5. Comments about pathology education in general

Survey responses were both quantitative and qualitative. Quantitative results were tabulated using Microsoft Office Excel 2003 (Seattle, WA). Qualitative responses were analyzed using a general inductive approach,[16] which allows important themes to be highlighted from open-ended responses.

Results

Preclinical Pathology Education

In nine of 16 schools (56%), pathology was taught as a separate discipline. The remaining schools incorporated pathology within integrated systems or blocks. Despite this integration, in 15 schools (94%) the Department of Pathology retained either "total" or "significant" control of its own teaching content. However, when asked to describe the degree of influence over "overall curricular design or content," only three schools (19%) reported "major" influence. For 50% of respondents the degree of influence was limited to "some," while 31% described "minimal" influence.

A large majority of schools (88%) had a single pathologist who was responsible for overseeing preclinical pathology education. The same proportion (88%) made use of pathology residents to help teach medical students, but only half of these schools had formal instruction for residents in teaching methods.

Curricular change was a very frequent experience for pathology educators: 88% reported significant changes in the medical curriculum at their school over the past 10–20 years. The most common change was replacing the traditional pathology course with an integrated non-discipline-based approach. Other frequently cited changes were reductions in the number of teaching hours and more emphasis on small-group teaching as opposed to large class lectures. One respondent, describing the reduction in pathology hours and the simultaneous transition from lectures to small groups, explained that "lots of low-quality contact with one pathologist [had evolved into] a little bit of high-quality contact with many pathologists."

The number of preclinical pathology contact hours was quite variable but overall lower than would have been the norm a generation ago: an average of 45 total lecture hours (range 5–140), 34 small-group hours (range 0–250), and a small amount of "other" time (average 2 hours, range 0–24 hours). The average total pathology contact time was therefore approximately 81 hours.

Every school made use of photomicrographs to teach pathology, and 94% of schools used photographs of gross specimens. Only half of the respondents reported the use of gross tissue itself for teaching. Half of the schools used digital (virtual) microscopy, with actual microscopes being used by only three schools. Autopsies were used educationally by only two schools.

Almost every school (94%) indicated that they did not try to teach medical students how to make a histopathological diagnosis. Instead, there was general agreement that medical students should primarily focus on learning pathogenesis, rather than diagnostic pathology as taught to pathology residents. The majority of respondents described using pathology and pathology images to illustrate and reinforce basic concepts of disease. One third of respondents added that they emphasized how pathologists contribute to clinical care.

Pathology Electives

Ninety-four percent of schools had pathology electives during the clinical year(s), and just over half made rotations available for preclinical students. Two schools had some kind of mandatory rotation in pathology. In half of the schools, pathology was actively promoted to medical students who were choosing electives.

Pathology as a Career Choice

Seven respondents (44%) indicated that pathology was definitely recognized as a valid career choice by their medical students. At three schools (19%), pathology had "some career exposure" and was "possibly" recognized as a potential career. At six schools (38%), pathology was mostly not recognized as a career. Thirteen schools had some kind of career outreach or recruitment program. Only one school

had any kind of student interest group or club for pathology.

Student Feedback about Pathology Teaching

Almost every school (94%) solicited individual instructor evaluations from its medical students. A large majority (81%) also gathered overall student feedback about pathology teaching. Eleven schools described the results of this overall feedback: every response described "excellent ratings" or otherwise-positive feedback, and at two schools pathology was the "best" or "highest-rated" preclinical experience.

Comments about Pathology Education in General

Thirteen respondents contributed their own perspectives about pathology education in general. The most common theme, cited by five respondents, was that pathology teaching should be increased. Some respondents reiterated that teaching should focus on pathogenesis and not histopathological diagnosis. The importance of learning pathology was emphasized; however, two respondents pointed out that pathology faces institutional resistance in some medical schools.

Discussion

Pathology education is a foundational component of medical education for generalist physicians. Although this perspective was uncontroversial in Flexner's time[7] and modern pathology educators have continued to defend it,[2,5,6] Canadian and international curricular trends over the past 20 years seem instead to emphasize communication skills and social responsibility.[17] However, recent publications in the United States and Canada suggest that both countries may soon see a renewed emphasis on the basic medical sciences, including pathology.[8,9]

Despite this potential for optimism, it is clear that the curricular pendulum has not yet swung very far in pathology's direction. Many schools have lost pathology courses in favour of an integrated interdisciplinary approach, and most schools now have very limited pathology contact hours. In general, pathology educators do not feel that they have a major influence over the medical curriculum.

The reduced pathology contact time in Canada mirrors the situation in the United States, where average pathology hours fell from 250 in 1986 to 188 just 10 years later.[13] The current Canadian average is less than half that. There is, of course, more to pathology education than simply the number of hours: as many respondents indicated, Canadian pathology education has shifted from a mostly didactic activity in a large class to interactive small-group teaching. Student feedback about these small-group pathology sessions is positive, as has been shown previously.[18] Small-group pathology teaching was described by one respondent as "a little bit of high-quality contact with many pathologists," and it appears that medical students share this opinion about quality.

American data[15] suggest that neither the presence of a formal pathology course nor increased pathology contact hours is correlated with better student performance on pathology examinations. Taylor et al.[15] suggest that it may be enough for pathology to "control" its own teaching, even in the absence of a specific pathology course. Interestingly, at nearly every Canadian school, the Department of Pathology still retains total or significant control over its educational delivery, whether in the form of a pathology course or within an integrated multidisciplinary unit.

Most Canadian pathology educators do not make use of autopsies or gross pathology specimens in their teaching. Instead, pathology is primarily taught to medical students using gross photographs and photomicrographs, as well as virtual microscopy. Likely reasons for this include not only reductions in available time but also cost and convenience. It can be difficult and expensive to retain gross specimens for teaching; it is also increasingly difficult to arrange for students to attend autopsies, as class sizes increase and as hospital autopsy numbers dwindle.

Almost every medical school offers clinical rotations in pathology to its clerkship students, and a majority promote these elective opportunities in some way. However, only 44% of respondents indicated that pathology was definitely recognized as a career choice at their school, and at almost as many schools, pathology was described as having limited career recognition. Given the importance of and the difficulty in recruiting more students into pathology,[10,11] these findings are alarming but not unexpected. For pathology to recruit more students, it will need considerably better exposure.

Many Canadian pathology educators are troubled by the limited contact hours with students and believe that there should be more pathology teaching than there is now. Some respondents thought that this should happen during clerkship rather than just through more preclinical lectures. Many respondents also emphasized the importance of introducing pathology as a career. Unfortunately, pathology faces "institutional resistance" at some schools, where pathology as a subject may be underemphasized and pathology as a career may be ignored. It will likely fall to Departments of Pathology, rather than Faculties of Medicine, to take responsibility for improving pathology's medical school profile.

One finding deserves to be emphasized: pathology education for Canadian medical students focuses on teaching *pathogenesis* rather than *diagnostic pathology*. This pathogenetic focus is certainly justifiable: our students will almost all become clinicians rather than pathologists and the teaching of clinically relevant diagnostic pathology can easily be deferred until residency. Clinicians-in-training obviously need to learn fundamental concepts of disease,[8,9] which pathologists are uniquely qualified to teach; just as clearly, most students do not need to learn diagnostic histopathology as a discipline. For example, future family physicians and internists should be expected to know the difference between *benign* and *malignant* but perhaps not the specific morphological criteria that differentiate adenoma from adenocarcinoma. This seems to be the consensus among pathologist educators in Canada. It is interesting that what is "obvious" to one generation of medical educators may appear unnecessary to the next generation. Discussions with senior pathology educators seem to indicate that 20 years ago it was "obvious" that medical students should all learn diagnostic histopathology, albeit at a basic level (unpublished data, J. Ford).

Given some of the problems in Canadian pathology education (such as limited teaching hours, ignorance of pathology as a career choice, etc.), it is important to note that pathology teaching remains consistently popular among Canadian medical students. They appreciate what pathologists teach them, and the quality of pathology teaching in Canada is generally excellent. If, to rephrase Osler, "as goes your pathology, so goes your medical education," the pathological foundation of medical education in Canada is well taught and is valued by our students.

Acknowledgements

We wish to thank our colleagues across Canada who willingly shared their expertise and opinions about pathology education.

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INVITED REVIEW

Precursors of Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Intraductal papillary mucinous neoplasms (IPMNs), intraductal tubular neoplasms (ITNs), and pancreatic intraepithelial neoplasia (PanIN) lesions are considered precursors of pancreatic adenocarcinoma. They are divided according to the size of the lesions and morphological features. IPMNs are classified according to the type of epithelium lining the papillae, and IPMNs, ITNs, and PanINs are also graded according to the severity of dysplasia. They can be distinguished by characteristic immunoprofiles with respect to mucin and genetic changes. In this review, the main morphological and molecular features are presented.

RÉSUMÉ

La tumeur intracanalaire papillaire mucineuse, la tumeur intracanalaire de structure tubulaire et la néoplasie intraépithéliale pancréatique sont des lésions précancéreuses susceptibles d'évoluer vers l'adénocarcinome pancréatique. Ces lésions sont réparties en fonction de leur taille et de leurs caractéristiques morphologiques. Les tumeurs intracanalaires papillaires mucineuses sont classifiées selon le type de revêtement épithélial de la papille, et les tumeurs intracanalaires papillaires mucineuses, les tumeurs intracanalaires de structure tubulaire et les lésions néoplasiques intraépithéliales pancréatiques sont aussi classées en fonction de la gravité de la dysplasie. Elles se distinguent également par leur profil immunologique particulier en ce qui a trait à la mucine et aux changements génétiques. L'étude présente les caractéristiques morphologiques et moléculaires principales.

Three precursors of pancreatic ductal adenocarcinoma have been described. They are divided into intraductal papillary mucinous neoplasms (IPMNs), intraductal tubular neoplasms (ITNs) and pancreatic intraepithelial neoplasias (PanINs), according to the size of the pancreatic ducts from which they arise and their morphological features. Although this classification is helpful in the study of the precursor lesions, it is not always easy to separate these lesions and the definitions do not encompass the full spectrum of lesions encountered.

Intraductal Papillary Mucinous Neoplasms

IPMNs are a distinct group of neoplasms originally defined according to the World Health Organization (WHO) as intraductal papillary mucin-producing neoplasms, arising in the main pancreatic duct or its major branches. The

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papillary epithelial component and the degree of mucin secretion, cystic dilatation, and invasiveness are variable. By definition, IPMNs lack the "ovarian"-type stroma seen in mucinous cystic neoplasms. A consensus meeting later resulted in a revised definition: "grossly visible, non invasive, mucin-producing, predominantly papillary, or rarely flat, epithelial neoplasms arising from the main pancreatic duct or branch ducts, with varying degrees of ductal dilatation. The IPMNs usually produce a lesion >1cm in diameter and include a variety of cell types with a spectrum of cytologic and architectural atypia."[1]

The neoplasms are rare, comprising only 5% of exocrine pancreatic tumours. Adults are affected with a mean age at diagnosis of 63 years age (range 25–94 years) and a male-to-female ratio of 3:2. Approximately one third of patients have a history of an associated neoplasm, especially colonic and gastric malignancies. IPMNs have also been described in patients with Peutz-Jeghers and familial polyposis syndromes. The majority of cases are asymptomatic and are detected incidentally by imaging studies. When symptoms are present, they are usually non-specific: epigastric pain, weight loss, and pancreatitis.[2] IPMNs are localized in the head of the pancreas in 70–80% of cases, are multifocal in 20–30%, and involve the entire ductal system in 5–10%. Typically these lesions are radiologically identifiable as a dilatation of the main duct ("main duct type"), the secondary ducts ("branch duct type"), or both ("mixed type").[2] The criteria to distinguish main duct–type from branch duct–type IPMNs are not well established and require pathological and radiological correlation. This distinction has clinical implications since the main duct type is frequently associated with an invasive adenocarcinoma, most often of colloid type. The branch duct–type IPMNs represent approximately 30% of cases, occur in younger patients, contain low-grade dysplasia, and are associated less commonly with invasive adenocarcinoma.

Macroscopic Findings

IPMNs are cystic lesions and are variably filled with thick mucin. In the main duct type, the entire duct system may be involved and appears tortuous, whereas if the branch ducts are involved, the lesion may be multiloculated. The papillae range from delicate granularities to friable intraluminal masses. The size varies from <1 cm to the entire pancreas. IPMNs with an invasive component tend to be larger in size, although size cannot be taken as the only indicator of invasion. Solid and gelatinous nodules also indicate probable invasion. The parenchyma surrounding the lesion is pale and fibrotic as a consequence of obstruction and pancreatitis. Large IPMNs can comprise multifocal areas of high-grade dysplasia, as well as small invasive carcinomas, even in the absence of a defined mass. Therefore, careful macroscopic examination of all IPMNs and extensive, if not complete, sampling are suggested. Solid and gelatinous nodules should be sampled first. If high-grade dysplasia is found without invasive carcinoma, the entire specimen should be submitted.[2]

Microscopic Findings

In the WHO classification, IPMNs are graded into various categories according to the degree of cytoarchitectural atypia present, and grading of dysplasia is based on the most severe degree found in a well-sampled lesion. IPMN-adenomas consist of tall and mucin-producing cells with minimal dysplasia. IPMN-borderline tumours harbour moderate dysplasia characterized by a moderate loss of polarity, nuclear crowding, nuclear enlargement, pseudo-stratification, and hyperchromasia. True papillae are present; however, pseudopapillary structures may also be seen. Intraductal papillary mucinous carcinoma includes IPMNs with severe dysplasia (carcinoma in situ [CIS]) even in the absence of invasion. The architectural features include true well-developed papillae and micropapillae. Cytological features of severe dysplasia comprise a loss of polarity, a reduction of cytoplasmic mucin, including a complete loss of mucin, nuclear pleomorphism, nuclear enlargement, and the presence of easily found mitoses.

In addition, IPMNs are lined by different cell types that express specific types of mucin protein (MUC). According to the type of epithelium, IPMNs can be classified into four types: intestinal, pancreatobiliary, gastric, and oncocytic.

Intestinal-Type IPMNs

Intestinal-type IPMNs are the most frequently reported type (35%), and lesions may reach a large size (up to 5.5 cm). CIS is present in 85% of the cases, and these IPMNs are

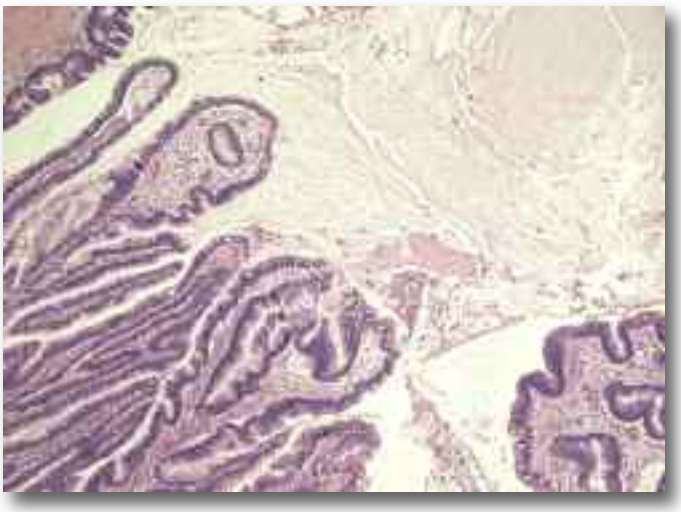

Figure 1. Intestinal-type IPMN consists of long finger-like projections. The epithelium is columnar, and the cells contain a variable amount of mucin in the apical cytoplasm. Goblet cells are easily identified. These lesions resemble colonic villous adenomas. (Hematoxylin and eosin)

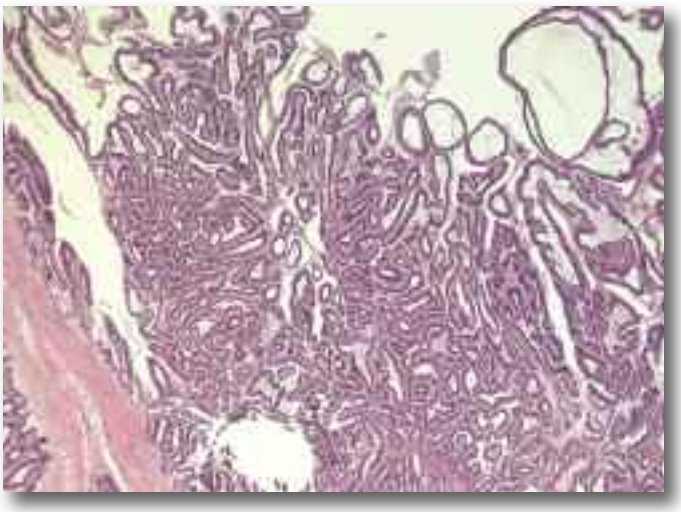

Figure 3. Gastric-type IPMNs resemble the foveolar gastric epithelium; the glands are lined by tall columnar cells with abundant pale supranuclear mucin with some cytoplasmic acidophilia. (Hematoxylin and eosin)

associated with invasive carcinoma in 62%, which is of colloid type in 87%. Most intestinal-type IPMNs are located in the pancreatic main duct.[3] The neoplasms are composed of long finger-like projections, lined by columnar cells containing pseudostratified, cigar-shaped nuclei with varying degrees of atypia and a variable amount of mucin in the apical cytoplasm. These neoplasms are morphologically indistinguishable from colonic villous adenomas.[4] Goblet cells, neuroendocrine cells, and Paneth cells are commonly seen (Figure 1).[2] The intestinal type expresses diffusely cytoplasmic mucin *MUC2* in 88% of cases, while *MUC1* is positive only in 8%. The majority of the intestinal-type IPMNs also express a specific marker of intestinal differentiation, *CDX2*, in 95% of cases.[4]

Pancreatobiliary-Type IPMNs

Pancreatobiliary-type IPMNs are similar to the papillary lesions arising in the biliary tree (see Figure 2 at http://www.cap-acp.org/index.cfm).[4] They comprise 22% of the cases, with an average size of 4.0 cm. The majority (94%) contain CIS and are associated with invasive carcinomas in 56%, of which 77% are conventional ductal adenocarcinomas. The neoplasm is composed of complex arborizing papillae with micropapillae and cribriform areas, lined by cuboidal cells containing round nuclei with a single prominent nucleolus. *MUC1* is positive in 44% of cases with focal *MUC2* expression in 19% of cases, while *CDX2* expression is uncommon.

Gastric-Type IPMNs

Gastric-type IPMNs are frequently located in the branch duct (98%) and comprise 31% of cases; approximately half the cases are adenomas with mean size of 2.6 cm. Invasive carcinoma is uncommon (17%).[3] They are composed of tall columnar cells with abundant pale supranuclear mucin with some acidophilia, resembling the gastric foveolar epithelium or the mucinous changes seen in low-grade PanIN (Figure 3).[4] Pyloric gland-like structures, consisting of two or three glands lined by columnar epithelium, are frequently seen and are located at the base of the papillae. There may also be PanIN-like complexes characterized by a collection of small ducts lined by tall columnar mucinous cells. These lesions express *MUC5AC* in the majority of the cells lining the papillae, as well as *MUC6* at the base of the papillae and in the pyloric gland-like structures. *MUC1* and *MUC2* are negative.[3,4]

Oncocytic-Type IPMNs

The mean size of oncocytic-type IPMNs is 6 cm, and these neoplasms are located more frequently in the head of the pancreas (72%), with a gross multilocular appearance. The dilated ducts are filled with soft red-brown nodular masses.

Invasive carcinoma has been reported in 18% of cases studied.[5] The neoplasms consist of complex papillae with a delicate core, lined by one to multiple layers of mostly oxyphilic, relatively bland cells with abundant granular cytoplasm (see Figure 4 at http://www.cap-acp.org/index.cfm). The nuclei are large and round with smooth contours and finely dispersed chromatin, and prominent nucleoli and mitoses are detected easily (see Figure 5 at http://www.cap-acp.org/index.cfm). There are small cystic spaces and lumina often containing mucin, which give rise to a cribriform pattern. Gastric foveolar type cells are uncommon, while scattered goblet cells are frequent. These lesions are diffusely positive for *MUC1*, whereas the goblets cells present stain for *MUC2* and *MUC5AC*.[2]

Unclassifiable IPMNs

Unclassifiable IPMNs cannot be categorized into any of the previous types or consist of a combination of two distinct patterns. This type represents approximately 12% of cases.[4] If multiple sections are taken, more than one type of epithelium is often identified and IPMN is named after the dominant epithelium present.

Pathways of Carcinogenesis

Thus, two major pathways of carcinogenesis can be defined and correlated with *MUC* expression. One is the intestinal pathway that comprises the intestinal-type IPMNs that express *MUC2* and *CDX2* but not *MUC1* and gives rise to colloid carcinomas that express the same markers. The second pathway is the tubular pathway that comprises pancreatobiliary-type epithelium and PanIN, which express *MUC1* but not *MUC2* and *CDX2*, and gives rise to tubular-type carcinoma.

Carcinoma is present in 35% of cases of IPMN. When adenocarcinoma is present, it should be graded and staged as a separate lesion from the IPMN. Invasive carcinoma can be multifocal, ranging from microscopic invasion to a predominant component with a residual intraductal component. When the invasive component is multifocal, determination of the size for staging purposes may be difficult; the largest single dimension measured microscopically should be reported rather than sum of the diameters of multiple foci. The concept of "minimally invasive carcinoma," although not clearly defined, may be used for invasive carcinomas measuring 0.5 cm or less.[2] Minimally invasive carcinomas have a better outcome: they are not associated with lymph node metastasis, unlike invasive carcinomas, which have a high rate of nodal metastasis (68%). In addition, they have a lower recurrence rate (2.5%) compared with invasive carcinomas (52%). Recurrence occurs in the remnant pancreas, reflecting the multifocality of the process.[6]

Molecular Studies

Molecular abnormalities have been reported in IPMNs. *KRAS2* mutations are an early event in the multi-step progression of these neoplasms, and the prevalence increases with the histological severity of the IPMNs.[7] They have been reported in all histotypes of IPMNs with the exception of the oncocytic type. The KRAS protein is a GTPase and is an early player in many signal transduction pathways, regulating cell-cycle progression via the mitogen-activated protein kinase (MAPK) and AKT cascades. Activating mutations of the *KRAS* gene result in a constitutively active protein.

On the other hand, loss of the *MADH4/SMAD4/DPC4* gene is infrequent in IPMNs and is seen only in the invasive component. *MADH4/SMAD4/DPC4* is a suppressor gene localized on chromosome 18q21 that encodes for a protein, DPC4, involved in the transforming growth factor β (TGF-β) signalling pathway. Loss of DPC4 results in decreased growth inhibition and uncontrolled proliferation. Inactivation of the Peutz-Jeghers syndrome gene, *STK11/LKB1*, is found in up one third of IPMNs but rarely in PanINs and associated adenocarcinoma. PI3KCA-activating mutations have been described in IPMNs. *PI3KCA* is a key protein in the AKT signalling pathway, frequently mutated in colonic cancer. The similarities between intestinal-type IPMN and colonic cancer are more than morphological.[7]

Chromosomal aberrations, consisting of copy number alterations, are frequently demonstrated in IPMNs with moderate- and high-grade dysplasia but not in IPMNs with low-grade dysplasia. Commonly lost regions are located on chromosomes 5q, 6q, 10q, 11q, 13q, 18q, and 22q. In addition, the incidence of loss of chromosomes 5q, 6q, and

11q is significantly higher in IPMNs with high-grade dysplasia or invasion than in pancreatic adenocarcinoma.[8] Telomeres are hexameric repeats located at the end of the chromosomes arms that confer stability on chromosomes during cell division. Progressive telomere shortening occurs early in the genesis of IPMNs, with the average length decreasing with IPMN progression. Even IPMN-adenomas demonstrate a 50% reduction of telomere length. Marked telomere shortening is observed from the IPMN-CIS stage through to the invasive carcinoma stage.[9]

Intraductal Tubular Neoplasms

ITNs include intraductal tubular adenomas and carcinomas. Tubular adenomas are uncommon tumours reported for the first time in 1992[10] and are morphologically similar to pyloric type adenomas of the gallbladder. Carcinomas have a similar morphological appearance but with significant cytological atypia. Macroscopically, the lesions are solid, solitary, polypoid, tan-coloured, friable excrescences occluding the lumen of the main pancreatic duct. The pancreatic duct distal to the intraluminal masses is dilated and contains mucinous material. The surrounding pancreatic parenchyma shows features of chronic inflammation and fibrosis. Histologically, the proliferations are composed of closely packed ducts or glandular structures lined by cuboidal to columnar cells with basal nuclei. The cytoplasm varies in amount with obvious mucin resembling that of pyloric-type glands. Minimal cytological atypia is present (Figure 6). The surrounding pancreatic ducts are mildly dilated and often replaced by low-grade pancreatic intraepithelial neoplasia (PanIN-1A and PanIN-1B), including metaplastic pyloric glands.[11] The tubular adenomas are immunoreactive for *M-GGMC-1* and *MUC6* and also, although less prominently, for human gastric mucin and *MUC5AC*.[4,11,12]

Intraductal tubular carcinomas have moderate to marked cytological atypia and contain less mucin. Mitoses are easily identifiable, and necrosis can also be present. Invasive carcinoma has been reported in two thirds of the cases and consists of small, angulated non-mucinous glands associated with a desmoplastic reaction in the adjacent tissue surrounding the duct.[2]

Gastric-type IPMN has been found associated with intraductal tubular adenoma in the same pancreatic duct or in the immediate branches, as well as with PanIN-1A and -1B in the smaller ducts. Intraductal tubular adenomas coexist with IPMN in 50% of cases within the same duct or in separate ducts that are close by. In the other cases without a coexistent IPMN, the intraductal tubular adenomas occur within a main duct that is lined by normal pancreatic epithelium. It is possible that these intraductal tubular adenomas arise from a small focus of gastric/pyloric metaplasia and grow into the lumen without radial extension along the circumference of the duct. From this, one can speculate that intraductal tubular adenoma occurs in two settings: without IPMN and with gastric-type IPMN.[13]

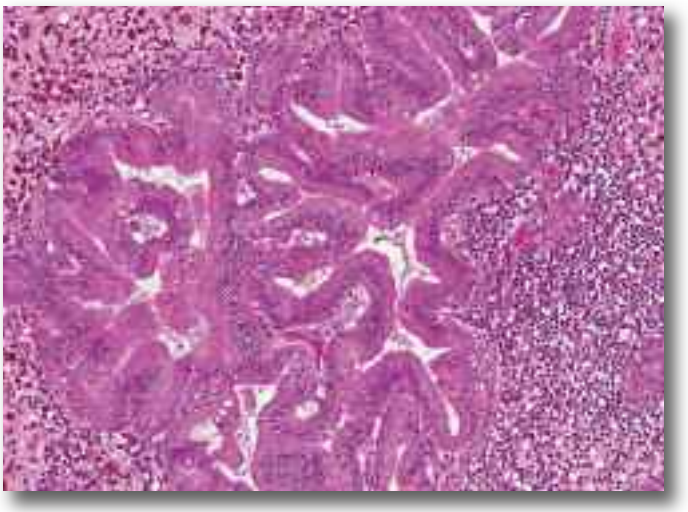

Figure 6. Intraductal tubular adenoma consists of cuboidal to columnar cells with basal, round to oval nuclei and eosinophilic cytoplasm. The glands are surrounded by florid granulation tissue and hemosiderin deposits secondary to torsion. (Hematoxylin and eosin)

Pancreatic Intraepithelial Neoplasia

PanIN was described over 100 years ago. However, the study of these lesion was hampered until the nomenclature first proposed by Klimstra and Longnecker[14] allowed uniform histological criteria for grading these lesions.[1,15] PanIN is defined as a microscopic papillary or flat, non-invasive epithelial neoplasm arising in the pancreatic ducts. The lesion consists of columnar to cuboidal cells with variable mucin and cytological and architectural atypia. PanINs usually arise in pancreatic ducts smaller than 0.5 cm. The size of the duct should be measured from the basement

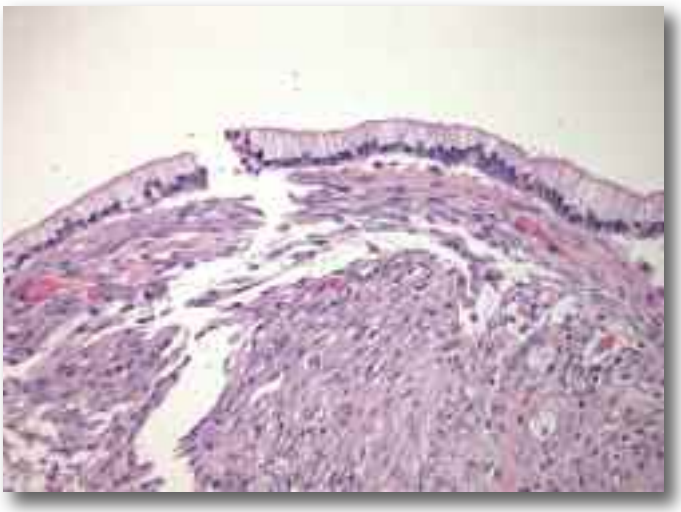

Figure 7. PanIN-1A consists of tall columnar cells with basal nuclei and abundant supranuclear mucin. The nuclei are small and round to oval. The atypia is minimal. (Hematoxylin and eosin)

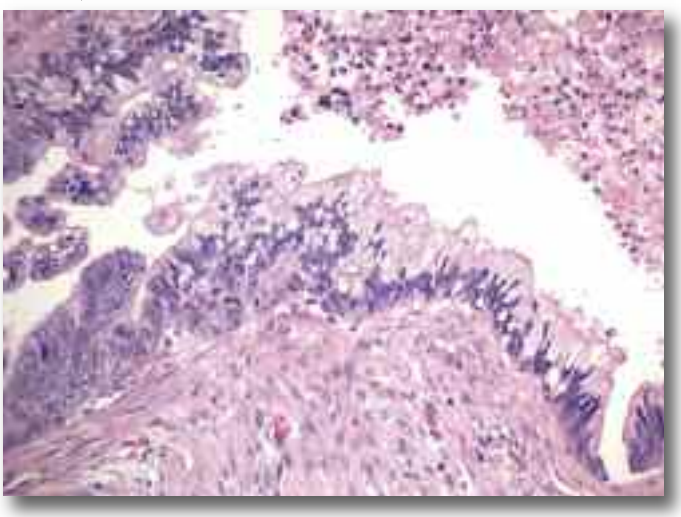

Figure 9. PanIN-2 lesions *(right)* may be flat or papillary and show nuclear abnormalities, including some loss of polarity, crowding, enlargement, pseudostratification, and hyperchromasia. PanIN-3 lesions *(left)* are usually papillary or micropapillary, although they may rarely be flat. There is loss of nuclear polarity, nuclear irregularity, and prominent nucleoli. (Hematoxylin and eosin)

membrane, while periductal fibrosis and small periductal glands or ductules, even if involved by PanIN, are not included in the measurement. When the duct is larger than 0.5 cm in diameter, it is usually secondarily dilated from obstruction by a proximal mass or stricture.

PanIN lesions are graded PanIN-1, PanIN-2, and PanIN-3, depending upon the degree of cytological and architectural atypia. PanIN-1 is the lowest grade of lesion and is divided into PanIN-1A and PanIN-1B based on the presence or absence of intraluminal papillae. The atypia is minimal.

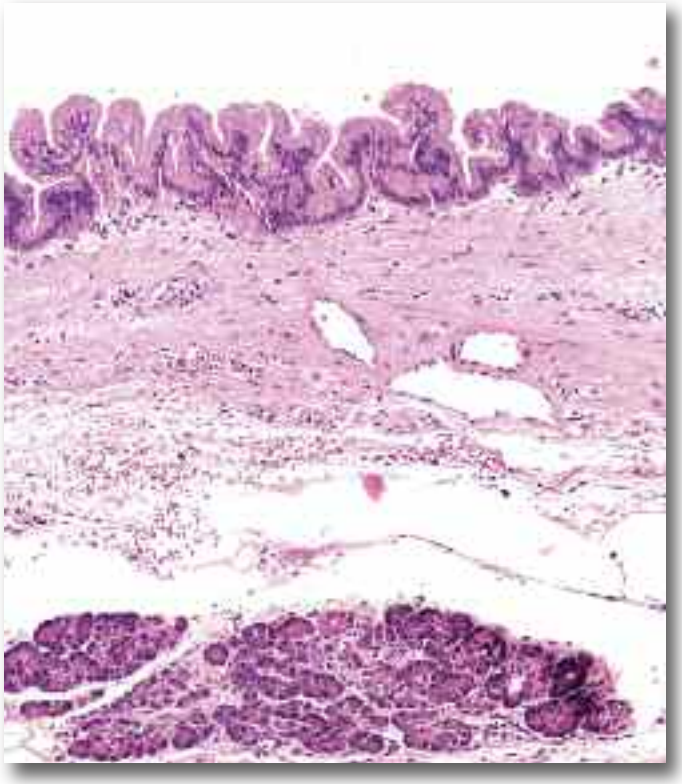

Figure 8. PanIN-1B lesions have a pseudostratified architecture, but are otherwise identical to PanIN-1A lesions. (Hematoxylin and eosin)

Cells are columnar with basal nuclei and apical mucin (Figures 7 and 8). PanIN-2 lesions have a moderate degree of atypia. These lesions must have some nuclear abnormalities, such as a mild loss of polarity, crowding, enlargement, pseudostratification, and hyperchromasia. Mitoses are rare and, when present, are not apical or atypical. The architecture is most frequently papillary (Figure 9). PanIN-3 lesions have severe atypia. The architecture may be papillary or micropapillary, with a cribriform appearance and frequent intraluminal necrosis. Nuclear atypia, prominent nucleoli, and dystrophic goblet cells are seen. Mitoses are frequent and may be abnormal (see Figure 9). These lesions are considered CIS.[1] PanIN is a non-invasive precursor of pancreatic ductal adenocarcinoma. There is evidence that high-grade lesions can progress to invasive cancer over a period of months or years. In addition, molecular studies have demonstrated that there are genetic abnormalities associated with the progression of these lesions.

Molecular Studies

Mutations in the *KRAS2* oncogene are seen in 90% of invasive carcinomas and are one of the earliest mutations found in PanINs (see Figure 10 at http://www.cap-acp.org/index.cfm). Their prevalence increases with progression of the lesions through PanIN-1A (36%), PanIN-1B (44%) and PanIN-2–3 (87%). In contrast, the frequency of *KRAS2* mutations is low (approximately 10%) in PanIN, arising in the background of pancreatitis. Most frequently, the mutations are in the codon 12 resulting in a constitutive activation of the GTPase activity of the protein.[16]

Inactivation of the *CDKN2A/INK4A* gene has also been documented. This gene is a tumour suppressor on chromosome 9p21 that encodes p16, an inhibitor of the G1-S transition in the cell cycle. A loss of the *CDKN2A/INK4A* gene can occur via several different mechanisms, including homozygous deletion, intragenic mutation with loss of the second allele, and epigenetic silencing by promoter methylation. Loss of function of p16 has been reported in 90% of pancreatic adenocarcinomas, with progressive loss in about 30% of PanIN-1, 55% of PanIN-2, and 71% of PanIN-3 lesions. Loss of p16 is also found in PanIN lesions arising in chronic pancreatitis (0%, 11%, 16%, and 40% for PanIN-1A, -1B, -2, and -3, respectively) and may explain the predisposition of patients with long-standing chronic pancreatitis to develop pancreatic adenocarcinoma.[16]

Inactivating mutations of *TP53* gene on chromosome 17 are found in 50–75% of pancreatic adenocarcinomas. Loss of p53 function is a late event in pancreatic adenocarcinoma development and may contribute to the genetic instability. Nuclear accumulation observed by immunohistochemistry is found exclusively in advanced PanIN-3 lesions with no overexpression seen in low-grade lesions.[16] Loss of the *MADH4/SMAD4/DPC4* gene function is infrequent in PanIN, only 31–41% in PanIN-3 lesions, and it is a late event in the progression pathway of pancreatic adenocarcinoma. Immunohistochemical labelling for DPC4 protein reflects the *MADH4/SMAD4/DPC4* gene status.[16] The caretaker gene *BRCA2* located on chromosome 13q, when mutated, predisposes to pancreatic cancer. It plays a role in homologous recombination repair in response to deoxyribonucleic acid damage induced by cross-linking agents. Germline mutations are found in 7–10% of patients with pancreatic cancer. It is rarely found in PanIN lesions.[16] Loss of heterozygosity (LOH) occurs particularly on chromosomes 9p, 18q, and 17p, regions also commonly altered in infiltrating pancreatic adenocarcinomas. There is evidence that LOH for a given locus increases with the grade of PanIN lesions, and there is a progressive selection of aggressive subclones in the intraductal component. The allelic loss may be the first hit in the two-hit inactivation process.[16] Loss of telomeric integrity is found in 90% of PanINs, even of low grade, resulting in secondary chromosome instability.[16]

Differential Diagnosis

There are accepted criteria to distinguish IPMN from PanIN lesions. IPMNs are macroscopically visible, can be detected radiologically, being usually larger than 1 cm, are mucin-producing, and form papillae. IPMNs usually arise from the main pancreatic duct or its branches. On the other hand, PanIN lesions are a microscopic, incidental finding, not radiologically detectable, <0.5 cm in size, and identified in smaller peripheral ducts. PanIN lesions are *MUC2* negative, and high-grade lesions show a loss of DPC4 in 30% of cases. Overlapping histological features can sometimes make the distinction between the two lesions practically impossible. Lesions between 0.5 and 1.0 cm can represent a grey zone since they may be branch duct IPMNs or a large focus of PanIN. In addition, these lesions usually consist of gastric-foveolar type epithelium that is negative for *MUC2*, even in the eventuality of gastric-type IPMN.

Another diagnostic problem can occur with the interpretation of a small intraductal lesion in a pancreas with clear IPMNs elsewhere. IPMNs and PanIN lesions can be found together in the same pancreas, and PanIN lesions may show a higher grade of dysplasia and contain a greater number of aberrations in protein expression than the IPMNs. IPMNs and PanIN lesions with the same grade of dysplasia share common aberrations in the expression of p21 (p21 binds to and inhibits the activity of cyclin-CDK2 or -CDK4 complexes and thus functions as a regulator of cell cycle progression at G1) and p16 and activating *KRAS* mutations, suggesting the existence of similar pathways in the progression of these two lesions. For example, a loss of DPC4 expression is found more frequently in PanIN-3

lesions associated with ductal adenocarcinomas than with IPMNs.[17] The possibility of IPMNs arising from PanIN lesions cannot be completely excluded, although there are differences in morphology, progression, and molecular phenotypes between these two types of lesions.

The differential diagnosis of IPMNs includes mucinous cystic neoplasms (MCNs). MCNs occur in young middle-aged females, are localized in the tail of the pancreas, may be multilocular with a thick wall, and do not communicate with the pancreatic duct. Histologically, MCNs show an ovarian-like stroma beneath the epithelium that is positive for estrogen, progesterone, and frequently also for inhibin.

Retention cysts are also included in the differential diagnosis. They are unilocular and lined by a single layer of non-mucinous cuboidal ductal epithelium with no cytological atypia. PanIN may occur in retention cysts (mucinous non-neoplastic retention cyst) with papilla formation, making the distinction from IPMN difficult. Multiloculation, the presence of papillae, or cytological atypia favour a diagnosis of IPMN.[2]

Conclusion

IPMN and PanIN lesions are well-recognized precursors of pancreatic adenocarcinomas. They have specific morphological and genetic features that can be helpful in distinguishing the lesions. However, there are rare cases where overlapping histological features make this distinction difficult. Gross, radiological, and clinical features can be useful to reach the correct diagnosis. Molecular aberrations may result in the activation of several epithelial differentiation pathways, playing a key role in the progression and in the phenotype of these lesions. Although ITNs are uncommon lesions, they have been recognized as precursors of pancreatic adenocarcinomas. Further studies are required to better characterize these lesions.

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The Schulich School of Medicine and Dentistry, The University of Western Ontario, London Health Sciences Centre and St. Joseph's Health Care London, invite applications/nominations for the position of Chair/Chief of the Department of Pathology.

The Department of Pathology has a long history of recognized excellence in diagnostic service, teaching, research and administrative leadership. Department members teach medical, dental and health sciences students at the undergraduate, graduate and postgraduate levels, and are engaged in many different areas of basic, clinical and translational research. The Department of Pathology and Laboratory Medicine includes anatomical pathologists, neuropathologists, oral pathologists, medical microbiologists, hematologists, medical biochemists and basic scientists. Members of the Department provide diagnostic pathology and laboratory medicine services for the clinical campuses of St. Joseph's Health Care and London Health Sciences Centre (University Hospital and Victoria Hospital) and referred in work from outside the local health network. London Health Sciences Centre is the site of the Regional Forensic Pathology Unit for Southwestern Ontario. The laboratory sections, excluding core laboratories, are consolidated to single sites eg. Pathology at University Hospital and Microbiology at Victoria Hospital.

The new Chair/Chief must have the vision to expand the strengths of integrated clinical, teaching and research programs aligned with the University, Lawson Health Research Institute, London Health Science Centre and St. Joseph's Hospital. He/she will be a strong administrator and excellent communicator and be able to advocate for the department's mission and goals, and an active researcher who can work collaboratively with basic and clinical scientists and non-laboratory medicine clinicians. The successful candidate must be an accomplished clinician with an MD or equivalent degree, must have certification in Anatomical or General Pathology from the Royal College of Physicians and Surgeons of Canada (or equivalent) and must be eligible for licensure in Ontario. A strong record of teaching, research and clinical service is required. Academic rank and contractual arrangements will be commensurate with experience and qualification.

London Ontario is a vibrant city of 350,000 people, originally settled in 1826 at the forks of the Thames River, boasts the University of Western Ontario with nearly 30,000 undergraduate and graduate students, the London Health Sciences Centre and St. Joseph's Health Care which serve a population base of more than 2 million southern Ontario residents. London has affordable housing prices and is close to the Great Lakes and outstanding outdoor recreational opportunities. The city has an active arts and sports community, international airport and is an easy commute to both Toronto, Ontario and Detroit, Michigan.

Interested candidates are encouraged to apply by the deadline of October 15, 2010 with CV, letter of application and the names and addresses of three references. The position will remain open until filled.

Dr. Nigel Paterson, Associate Dean, Clinical Academic Affairs &
Dr. Gillian Kernaghan, Integrated Vice President, Medical Education & Medical Affairs
C/o Heather Frankling
Selection Committee Coordinator
Schulich School of Medicine & Dentistry
Room 3720
The University of Western Ontario
London, Ontario N6A 5C1

Positions are subject to budget approval. Applicants should have excellent written and oral communication skills in English. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. The University of Western Ontario, London Health Sciences Centre and St. Joseph's Health Care London are committed to employment equity and welcome applications from all qualified women and men, including visible minorities, aboriginal people and persons with disabilities.

MOLECULAR ONCOLOGIC PATHOLOGY FELLOWSHIP PROGRAM in CANADA

Toronto, Kingston, Vancouver, Victoria, Calgary
Openings for 2010 - 11

"TFF STIHR* in Molecular Pathology of Cancer at CIHR" is funded jointly by the Terry Fox Foundation (TTF) and the Canadian Institutes of Health Research (CIHR). This is a specialized research training program for **"Clinician-Scientists in Molecular Oncologic Pathology"**, available at any of the four training centres:

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

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

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

For further information and application details please contact:

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

or

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

Website: http://molecularpathology.ca

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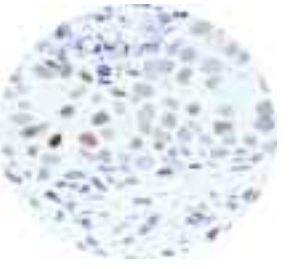

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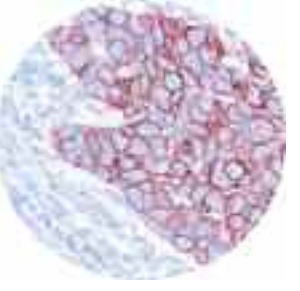

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