

## Happenings in Histopathology – A Post-World War II Perspective<sup>†</sup>

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### Abstract

There have been several important developments in the practice of histopathology since World War II; those reviewed in this lecture are grouped under 4 headings: new techniques (cytopathology, electron microscopy, immunohistochemistry and molecular pathology), organisational issues (recruitment, training and certification, subspecialties, quality control and consultations), ethical and legal issues (service costs, and the ownership and uses of biopsy tissues) and globalisation (international associations, standardised classification and nomenclature, and telepathology). Advances in the fields of molecular pathology and telepathology are expected to have the greatest impact on the practice of pathology in the next decade.

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### Introduction

During the past few decades, there have been many significant developments in the practice of histopathology, the specialty that is also referred to as anatomic pathology, surgical pathology, or simply as pathology without qualification. Those selected for review are grouped under 4 headings: new techniques, organisational developments, ethical and legal issues, and globalisation. World War II was a convenient starting point because it was almost immediately after the war, in the 1940s, that I began my career in this specialty. This will be a general review; it is not based on happenings in any particular institution or country.

### New Techniques

Up to the mid 20<sup>th</sup> century, histopathologic diagnosis was based mainly on tissue sections stained with haematoxylin and eosin (H&E) and a few supplementary stains. The techniques were simple, but those were great days for pathology. Many diseases were then defined and recognised on the basis of tissue changes. Pathology, the study of the morphology and mechanisms of diseases, was the epicentre of the medical school curriculum. “*As is your Pathology, so is your Medicine*” was one of Osler’s sayings that our teachers often quoted. Pathologists were the doctors’

consultants. Autopsies and pathology museums were pre-eminent in academic medicine. Those days have gone, they have gone forever.

The H&E remains the mainstay of diagnostic pathology to this day; it is our staple. New techniques introduced since World War II include cytopathology, electron microscopy, immunohistochemistry and molecular pathology.

#### *Cytopathology*

The technique of using cell smears instead of tissue sections for diagnosis was a subject of academic interest until it was validated for the diagnosis of uterine cancer in 1941.<sup>1</sup> This happened during World War II – after the war had broken out in Europe and before it had embroiled the Asia Pacific region. This technique has since been applied to exfoliated cells and needle aspirates from virtually all internal organs. Cytopathology has become a major component of the workload of pathology departments.

#### *Electron Microscopy*

Electron microscopy, introduced in the early 1960s, made important contributions to knowledge of cell structure but has not revolutionised the practice of pathology as anticipated. It is seldom used routinely except to resolve specific diagnostic problems

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### *Immunohistochemistry*

Immunohistochemistry, introduced in the 1970s, was a major advance. The range of commercially available antibodies with diagnostic and prognostic relevance has expanded exponentially. Few if any of these antibodies are as diagnostically sensitive or as specific as originally claimed, and some have even become useful markers for tissues other than those they were initially intended to recognise. Despite these limitations the use of immunological techniques in routine practice has undoubtedly improved the quality of histopathologic diagnosis.

### *Molecular Pathology*

The most momentous developments have occurred in the field of molecular medicine. Molecular and genetic techniques like the polymerase chain reaction (PCR), fluorescent in situ hybridisation (FISH), spectral karyotype imaging, DNA microarrays, and proteomics have many applications in diagnostic pathology. They have substantial applications in inherited genetic diseases, infectious diseases, transplant (chimerism) studies, lymphoproliferative diseases and solid tumours. More neoplasms are being defined by their molecular profiles and more molecularly targeted therapies are being developed. The urgent need for a molecular diagnostic service is not in question. It is the question of how this service should be organised that remains to be settled.<sup>2,3</sup>

Molecular techniques are not especially difficult or complicated. The availability of efficient PCR machines and test kits has already made them available to non-specialty laboratories; there may even be automated platforms for genetic assays in the near future. However, molecular profiling as a routine hospital service should be undertaken only by laboratories accredited for this function. Molecular diagnostic laboratories are best organised as part of the hospitals' own diagnostic services, and preferably within the administrative and functional framework of the pathology laboratories.<sup>2</sup> This would enable pathologists to adopt a combined histomorphologic, immunohistologic and molecular approach to tissue diagnosis and prognostication.<sup>2-4</sup> Pathologists participating in this service, in collaboration with molecular scientists, would have to undergo additional training in this field.

Advances in molecular diagnostic pathology have led to some speculation that conventional histopathology may soon lose much of its relevance and become obsolete. There is no realistic basis for such speculation. Molecular assays are not relevant in most biopsy diagnoses, and they are unlikely to have material impact on the validity and general applicability of conventional histopathology. Molecular assays provide vital supplementary information

on tumour biology, but they would not provide all the information needed for clinical decision-making.

## **Organisational Issues**

### *Recruitment*

There has been, during the past few decades, a remarkable increase in the proportion of women working as pathologists. This has happened because women have gained admission to medical schools in increasing numbers and also because women, mindful of their home and family commitments, have tended to prefer careers in specialties like pathology where working hours are more predictable than in the purely clinical disciplines. There was a time when it was assumed, quite mistakenly, that anatomic pathology, which was then heavily absorbed with autopsies, might not be a suitable career for women; such assumptions may well have influenced patterns of recruitment in the past.

### *Training and Certification*

In the first half of the 20<sup>th</sup> century, pathologists were trained mainly through apprenticeship; they were tutored by their mentors while working as their assistants. The introduction of formal courses of instruction leading to certification and accreditation to practice as pathologists began with the inauguration of Boards and Colleges of pathology in many countries. The American Board of Pathology was inaugurated shortly before the war, in 1936. The Royal College of Pathologists of Australasia, the Royal College of Pathologists of the UK and various Colleges and Societies of Pathology in several countries in Asia and Europe were inaugurated after the war.

Other post-war happenings that have boosted teaching and learning in pathology include the arrival of two-headed and multi-headed microscopes, the publication of some excellent textbooks and journals on various aspects of pathology and access to a vast amount of educational material on the internet.

### *Subspecialties*

Subspecialties in anatomic pathology have developed as a consequence of the enormous expansion of knowledge in this discipline. It had become too difficult for individual pathologists to keep abreast of advances in all aspects of pathology. They have also followed changes in the practice of medicine. Up to a few decades ago, the clinical services in most hospitals were directed by general physicians and general surgeons who were quite happy with the services provided by their counterparts, the general pathologists. These venerable characters, then the honchos of the hospital services, are now a dwindling breed. The clinical services in most large hospitals are now directed by the likes of nephrologists, gastroenterologists, neurosurgeons and

musculoskeletal surgeons. These specialists would like to have their biopsies reported exclusively by pathologists with corresponding sub-specialty expertise, and the pathologists who have acquired the necessary expertise have preferred to work exclusively within their subspecialty. It would be difficult for any but large laboratories employing more than about 20 pathologists to operate a subspecialty-based service. Smaller institutions have usually opted to employ general pathologists with special training and interests in one or more subspecialties. Various professional colleges and examination boards now provide additional training courses and certification for subspecialties like cytopathology, neuropathology, dermatopathology, oral pathology, paediatric pathology and molecular genetic pathology.

#### *Quality Control*

Quality control and patient safety have recently become subjects of prime concern in virtually all branches of medicine, and especially after the publication of the Institute of Medicine Report on this problem in 1999.<sup>5</sup> Errors and discrepancies in histopathology reports are not uncommon; they have been variously estimated to exist in some 1% to 5% of all reports, depending on the methods used for error detection and on the definition of what counts as an error.<sup>6</sup> Some of these are cognitive diagnostic errors but most are attributable to operational causes, like inadequate histories, contamination by extraneous tissues and clerical errors in labelling specimens and typing reports. Several investigators and the Association of Directors of Anatomic and Surgical Pathology (ADASP) have identified and analysed the sources of such errors and have formulated strategies for their reduction.<sup>7-9</sup> Most laboratories have committees to audit the accuracy of their reports.

The adequacy and completeness of pathology reports have also come under consideration. Until recently reports on malignant neoplasms consisted of the pathologist's diagnosis, a brief description of pertinent histological features and possibly some comments applicable to the case in question. Such individual-style reports have been largely replaced by checklists recommended by the College of American Pathologists (CAP) and ADASP; pathology reports have thereby become more complete and standardised. Pathologists also have access to computerised algorithms and support systems that assist them in making diagnostic decisions and generating reports.

The accuracy and completeness of histopathology reports are qualities that are difficult to define except in relative and judgemental terms.<sup>7,9</sup> Diagnostic criteria for some pathological entities are updated periodically; differences of opinion among pathologists are not always indicative of diagnostic errors. Moreover, errors and discrepancies in

histopathology are more likely to be discovered than in most other branches of medicine. The materials on which diagnoses are based, like glass slides and paraffin blocks, are often retained by laboratories for a minimum of 10 years, as has been recommended,<sup>10</sup> and are available for peer review whenever the rendered diagnosis does not match the clinical outcome. Under these circumstances, it is gratifying to note that malpractice suits in histopathology are relatively uncommon; medical insurers have categorised pathology as a low-risk specialty.

#### *Consultations*

Pathologists often consult their colleagues to get their opinions and to share the diagnostic responsibility on difficult cases; these second opinions are usually provided by consultants in the same laboratory. Consultations with pathologists in other institutions and other countries are also fairly common. These "outside" consultations were usually provided gratis in the past but are now often charged consultation fees – not because consultants have become more money minded but mainly because they are subject to their institutional guidelines on this question. Most institutions have fee schedules for pathology consultations just like for case referrals in other specialties. At any rate, pathologists and institutions who collect fees from their patients for reports like "*Diagnosis deferred – pending consultation*" should not be too disappointed if they are billed for the consultations.

Apart from consultations, second opinion reviews also occur when patients are transferred from one hospital to another.<sup>10</sup> ADASP and the American Society of Clinical Pathologists have recommended such reviews for all non-emergency cases for which major therapeutic interventions are planned.<sup>11,12</sup>

#### **Ethical and Legal Issues**

##### *Costs*

Changes in healthcare financing have made it necessary for laboratories to adopt a cost-conscious, business-oriented approach in providing their services. It is now customary for various categories of histopathology examinations and ancillary tests to be priced and charged separately. The question of costs is essentially an organisational issue but it has also been considered to be an ethical one on account of suggestions that pathologists or laboratories may overutilise ancillary tests for financial gain rather than diagnostic concern.<sup>13</sup> There are no documented examples of such ethical lapses in anatomic pathology; the possibility of their occurrence would not exist in situations where salaries of pathologists are not influenced by the tests they conduct and where laboratory charges are levied only for tests that are diagnostically relevant. There would

undoubtedly be situations where pathologists could have achieved the same results with fewer tests, but the use of additional tests in specific situations could be an issue of individual judgment rather than ethics. Additional tests are sometimes carried out to avoid medico-legal consequences of missed or incomplete diagnoses; they are sometimes conducted in groups or panels to avoid delays in reporting. Unnecessary laboratory tests are of course wasteful, regardless of who is paying for them, and should therefore be monitored and corrected.

#### *Ownership and Uses of Biopsy Materials*

It is generally agreed that tissues received by laboratories for histology and all materials derived from them, like paraffin blocks and glass slides, should remain in the custody of the laboratory. Claims that biopsy materials are the property of patients have not been recognised in law. Existing laws recognise the autonomy of patients' decisions over their bodies but there is no statutory law or case law that clearly defines physical ownership of tissue specimens.<sup>14,15</sup> It is most unlikely that patients can have property rights over their tissues or secretions after they have been submitted, with their full knowledge and permission, for laboratory examination. It is the laboratories receiving the specimens who have custodial rights over them and the responsibility to submit them to such tests as may be necessary to reach a satisfactory diagnosis. There are occasions, now more frequent, when patients make requests for duplicate sections of their biopsies to obtain second opinions or because they are transferring to another hospital which requires a slide review before offering therapy. Pathology laboratories are obliged to accede to such requests.

The use of human tissue for research has become the subject of public inquiry in many countries. It is agreed that materials submitted for diagnosis may not be used for "research" without the patients' informed consent.<sup>14-16</sup> There is no question that research that is unrelated to the patients condition, research aimed at developing products from which the investigator or his laboratory may derive financial benefit or any commercial dealings involving biopsy materials should not be undertaken without the patients' knowledge and permission. Most institutions have regulations controlling the use of tissues for research and bioethics committees to ensure that researchers comply with them. It should be noted, however, that research in histopathology generally involves more detailed examinations of biopsy materials, often using recently acquired knowledge or technology, to identify tissue abnormalities that may be of diagnostic or prognostic significance in the disease in question. There should not be any ethical or legal requirement to secure patients' permission to undertake such studies as long as their

identities are not disclosed during the investigations or in any publication or presentation of the findings.

#### **Globalisation**

The word globalisation describes the worldwide integration of activities associated with a free flow of knowledge, capital, goods or services. Globalisation in histopathology would include activities like the formation of international associations, the formulation of standardised classification, nomenclature and coding systems, and the provision of globalised diagnostic services.

#### *International Associations*

Several international associations of pathology have come into being after World War II. The periodic congresses organised by the International Academy of Pathology, the World Association of Societies of Pathology and the international associations of various sub-specialties of pathology have enabled pathologists to adopt a global approach in advancing their specialty. Congresses organised by various national societies of pathology have also opened up to international participation.

#### *Standardised Classification, Nomenclature and Coding Systems*

National and international organisations have collaborated in efforts to standardise the classification and nomenclature of neoplasms. Between the two World Wars the Association Francaise pour l'Etude du Cancer published a series of monographs and atlases on human neoplasms. After World War II the Union Internationale Contre le Cancer (UICC) published an *Illustrated Tumour Nomenclature* in 6 languages. The National Academy of Sciences-National Research Council of the United States published a series of Atlases of Tumor Pathology through one of its subcommittees; these Atlases, colloquially called "AFIP fascicles" because they were printed at the Armed Forces Institute of Pathology, were widely used as references. It was the World Health Organization (WHO), however, that has been most effective in this endeavour. Between 1958 and 1975, WHO set up some 25 Reference Centres tasked with developing international classifications of tumours of various organ systems using standardised nomenclature and definitions. These classifications, developed by pathologists from many countries under the aegis of WHO's Cancer Unit, were published in a series of books titled "*International Histological Classification of Tumours*" and colloquially called the "Blue Books" because they had blue covers. After 2 editions of these books, WHO published a new series of books titled "*Pathology and Genetics*" which provide more comprehensive descriptions of tumours; these books, also written by pathologists from many countries, were produced under the aegis of WHO's

International Agency for Research on Cancer (IARC).

The International Statistical Classification of Diseases (ICD), used worldwide for the collection and publication of morbidity and mortality data, had its beginnings well before World War II. The ICD was published by the International Statistical Institute from 1893 to 1920, the Health Committee of the League of Nations from 1929 to 1938 and by WHO since 1946. The ICD, intended for general epidemiological analyses, is not well suited for histopathologic studies; neoplasms, for example, are coded by their sites of origin and not by histology.

National and international organizations have also collaborated in providing standardised coding systems for pathology, viz the *Manual of Tumor Nomenclature and Coding* by the American Cancer Society, the *Systematized Nomenclature of Pathology* and the *Systematized Nomenclature of Medicine (SNOMED)* by CAP and the *International Classification of Diseases for Oncology (ICD-O)* by WHO. By agreement with CAP, the morphology codes of ICD-O are incorporated in the neoplasm section of SNOMED. The coded nomenclature in SNOMED<sup>17</sup> and ICD-O<sup>18</sup> are used worldwide by pathology departments and cancer registries.

#### *Telepathology and Globalised Diagnostic Services*

When considering the implications of globalising the diagnostic services, it is important to distinguish between the primary diagnoses made by pathologists and the secondary diagnoses or second opinions obtained through consultations. Diagnostic services may be described as “globalised” when pathologists in other countries become involved in either the primary or secondary diagnoses. Globalised second opinions have existed for decades; globalised primary diagnosis is a more recent development. Diagnostic pathology may be globalised either through conventional methods of transportation and glass slide microscopy or by telepathology.

Telepathology is the practice whereby pathologists render diagnoses from a distance by viewing electronically transmitted images. The transmission routes include ordinary telephone lines, dedicated high-speed digital lines, satellites and the internet. Diagnostic telepathology may be based on any of 3 currently available systems: a “dynamic” system, a “static-image” system and “virtual microscopy”.

In the dynamic system, pathologists view images in real time by exerting robotic control over remotely located microscopes. Dynamic-robotic telepathology has been used primarily to provide intraoperative frozen section diagnoses to hospitals without resident pathologists.

In the static-image system, pathologists view images that have been selected, stored and forwarded to them. This system has been used mainly to obtain second opinions on

difficult cases. Telepathology workstations have been installed in more than a dozen countries.<sup>19</sup> There are also a few international telepathology networks like the Arizona-International Telemedicine Network, the iPath server located in the University of Basel and the UICC-Telepathology Consultation Center located in the Humboldt University in Berlin.<sup>20-22</sup> A major drawback in this system is its dependence on microscopic images and staining reactions that are pre-selected by referring pathologists; they may not always be of optimal quality and they may not always be fully representative of the lesion.

“Virtual microscopy” is a technique whereby entire glass slides are scanned and converted to digital data files or “virtual slides” whose characteristics, in terms of resolution and range of magnification, are comparable with those of glass slide microscopy. The virtual slides may be distributed as CD-ROMs or transmitted over the internet and be viewed on computer screens. The use of virtual microscopy in medical education, slide seminars and quality assurance programmes is well established; the use of glass slides and optical microscopes in such activities may soon be obsolete. Virtual microscopy, however, has not been widely used to globalise the diagnostic services because it would not ordinarily be cost-effective to do so. Its use in telepathology is being tested.<sup>23</sup>

The overall diagnostic accuracy of static-image telepathology is about 5% lower than that for glass slide microscopy. An analysis of 171 consultation cases submitted to the Arizona-International Telemedicine Network revealed that telepathologists rendered a diagnosis in 144 cases and deferred rendering a diagnosis in 27; the concordance between telepathology and glass slide microscopy was 88.2% (127 of 144 diagnoses) for all diagnoses and 96.5% for diagnoses that were clinically important.<sup>20</sup> An international validation study based on 200 cases obtained from a workstation in a French telepathology network, with 4 participating pathologists working independently (each reviewing 50 cases), found that the concordance between glass slide microscopy and static-image telepathology was 87.5%; the overall diagnostic accuracy, using a final consensus as the correct diagnosis, was 95.5% for glass slide microscopy and 88.5% for telepathology.<sup>24</sup> The diagnostic accuracy of static-image telepathology is much higher, almost equaling that of glass slide microscopy, for small specimens like prostatic core biopsies<sup>25</sup> and endoscopic mucosal biopsies;<sup>26</sup> it is lower for large or complex specimens where the handicap of dealing with pre-selected images is more critical. The diagnostic accuracy of virtual microscopy for renal biopsies is similar to that of conventional microscopy.<sup>27</sup>

Investigations on the validity of different modes of telepathology for different types of biopsy specimens should

take into account the diagnostic expertise of the participating pathologists. Accuracy in histological diagnosis, by whatever mode or method, depends far more on the professional competence of the pathologists rendering the diagnosis than on the technology they are using. It's the singer, not the song.

Telepathology is an acceptable medium for expert consultations; it is also a convenient one. It frees the referring pathologist from the hassle of packing and mailing glass slides and concerns over releasing blocks or slides that may be irreplaceable. It frees the consultant from coping with slides that may have got broken in transit and concerns over whether they have to be returned to the senders. And it certainly reduces consultation times – glass slides take days to reach consultants, digital images minutes.

The use of telepathology for primary diagnoses is an altogether different proposition because local pathologists, if any, would not be responsible for the rendered diagnosis. This situation would raise some legal questions in addition to the usual issues of validity and cost-effectiveness. Would hospitals in countries that do not permit pathologists to practice within their territories without local registration and accreditation allow them to practice from a distance through telepathology? Who would be legally responsible for any harm that may befall patients through diagnostic errors or breach of confidentiality? Would medical insurers indemnify pathologists for malpractice claims raised in other countries for errors made through telepathology?

Proponents of telepathology have postulated that it has much in common with teleradiology.<sup>23</sup> Telepathology and teleradiology do have similarities with respect to techniques of digital imaging and data transmission but they also have important differences. Radiologic diagnosis is commonly based on digital images and many radiology departments have become fully digitised and filmless. Pathology departments cannot become tissueless or slideless. Surgical specimens have to be grossly evaluated and sampled for histology and sections stained according to particular diagnostic requirements before they can be digitised for transmission. Moreover, the high resolution quality of images and the need for viewing over a wide range of magnifications are more critical in histopathology where the differential diagnostic considerations are far greater than in radiology.

The use of telepathology for routine diagnosis is technically feasible but the question of whether it could be beneficial would depend on individual circumstances. It would be an obvious choice for hospitals and countries without resident pathologists and for those without sufficient pathologists to deal with their workload, especially in areas where they may lack particular subspecialty expertise. It

should not be the preferred system for hospitals or countries with well-established laboratories and are striving to upgrade their professional services. Pathologists, in short supply worldwide, will relocate to wherever there is a demand for their professional expertise. Any wholesale outsourcing of the diagnostic workload will, in the long term, exacerbate rather than resolve staff shortages. The use of globalised telepathology for routine diagnosis would not ordinarily be cost-effective and it may, moreover, be associated with a variety of problems that may have adverse consequences on patient care.<sup>27,28</sup> Histopathology is a clinical service that goes beyond the issue of biopsy reports; pathologists also serve as consultants who interact with their clinical colleagues in the management of patients.

The use of telepathology for routine diagnosis, made possible by technological advances, is also propelled by commercial considerations. The driving forces are in some ways similar to those that have promoted medical tourism. The operational systems in telepathology, a by-product of the digital revolution and the internet, will of course be different. It is anticipated that globalised diagnostic services could be provided by virtual laboratories, high level communications centres, equipped with scanners and servers and staffed by panels or networks of expert consultants. Such an outcome would be regarded as a threat by some and by others as an opportunity. The institutions that would thrive in this environment will be those that can provide a service that is competitive in terms of both cost and quality. The quality of the service will depend not on the advanced technology that is easily available but on the hard-earned professional competence of the pathologists rendering the diagnosis.

### The Future

Glass slide sections may be expected to remain the basis of histopathology for the foreseeable future, but there may be a growing tendency for pathologists to view them on monitors rather than through conventional optical microscopes. There will probably be a trend for laboratories to have some of their slides digitised – in order to automate the measurement of specific tissue abnormalities or to expedite consultations with experts.

Immunohistochemical reactions will no doubt undergo further expansion and refinement. They will be used not only as diagnostic markers of cell lineage and tissue type but also, following recent discoveries of regulatory molecules and the manufacture of corresponding antibodies, as therapeutic biomarkers for prognosis.

There will be soaring demand for the use of molecular techniques in tissue diagnosis, especially in the field of oncology. Most large hospital laboratories may be expected to provide their own molecular diagnostic services.

The use of globalised diagnostic services through telepathology has begun and, depending on the scale of its adoption, will have an enduring impact on the practice of pathology. Hospitals and laboratories planning to utilise such services for their diagnostic workload should do so selectively and judiciously, taking into account their particular diagnostic needs and the resources available locally. Any indiscriminate implementation of a diagnostic telepathology system may have adverse effects on the care of patients.

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