

## REVIEW

# More than meets the eye: the changing face of histopathology

James C E Underwood

*The Medical School, University of Sheffield, Sheffield, UK*

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Underwood J C E

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## More than meets the eye: the changing face of histopathology

This personal reflection on trends in histopathology over the past 50 years draws upon experience of professional training and practice in the specialty in the UK. Developments during this period often resulted from new therapies (and their adverse effects) necessitating greater precision in the histopathological classification of disease, for which morphology alone can be insufficient. Conversely, histopathology has contributed to advances in our understanding of disease, leading directly to novel and more effective treatments. New infections, some involving histopathology in their discovery, have also led to fresh diagnostic challenges. Increasingly, patients have benefited from

fundamental changes in professionalism in pathology. Through audit, external quality assurance, continuing professional development, standardized reporting, and increasing specialization, the consistency and reliability of histopathological diagnoses have steadily improved. Regarding the specialty's future, some now see rivalry between the morphological and molecular approaches to diagnosis and classification, particularly for neoplastic disease. An integrated strategy led by the specialty is more likely to strengthen histopathology and ultimately to have the greatest benefit for patients.

Keywords: autopsy, biopsy, diagnosis, histopathology, molecular pathology

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## Introduction

What lessons can we learn from our specialty's past? Fifty years ago, was there any value in understanding how the specialty had developed since 1917? Perhaps not initially, but later we often did question the rationale of then current practices. Were some ways of working simply rituals—a legacy of what might have been clinically relevant decades previously, but now with little or no benefit for patients? And now, have we failed to grasp fully the proven or potential impact of molecular pathology on tissue-based diagnosis? Looking back, can we discern a trajectory of progress from which future developments in histopathology can be extrapolated?

## Changes in medical and surgical practice

'Medicine used to be simple, ineffective and relatively safe. It is now complex, effective and potentially dangerous.'<sup>1</sup>

During the 20th century, surgery became safer, but medicine became more dangerous. The increasing safety of surgery over that long timescale was undoubtedly attributable to improvements in anaesthesia, in antisepsis, in surgical techniques, and in perioperative care. In contrast, adverse drug reactions (ADRs) caused by prescribed medicines now account for a significant proportion of hospital admissions,<sup>2</sup> and, in one study, they accounted for ~3% of hospital deaths.<sup>3</sup> The scope of the histopathology of ADRs and other iatrogenic conditions is too diverse to be summarized here. Suffice to say that, when ADRs result in morphological changes, they are often diagnostically challenging. Mimicry of naturally occurring

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Address for correspondence: J C E Underwood, Cliburn Mill, Penrith, Cumbria CA10 3AW, UK. e-mail: jceu@shf.ac.uk

diseases is common, and the iatrogenic nature of the problem may become evident only from subtle histological features or from the clinical circumstances.

Immunosuppression, either intentional (e.g. in transplantation), inadvertent (e.g. undesired consequence of chemotherapy) or resulting from disease (e.g. AIDS) gave rise to a marked increase in opportunistic infections diagnosed in biopsies or at autopsy. Histopathological skills are also required for diagnosing and grading rejection in transplanted organs or graft-versus-host disease in patients in whom immunologically active cells have been transplanted.

New infections also impacted on histopathology, particularly in the later decades of the 20th century—human immunodeficiency virus and AIDS, human papillomavirus and cervical neoplasia, human herpesvirus 8 and Kaposi's sarcoma, and severe acute respiratory syndrome (SARS) coronavirus and SARS, among others. A notable achievement in histopathology during this period was Warren and Marshall's identification of *Helicobacter pylori* in gastric biopsies. This observation prompted fresh thinking about the pathogenesis of gastroduodenal inflammation and ulceration,<sup>4</sup> and, of course, significantly contributed to a considerable increase in biopsy workloads.

Prosthetic joints have transformed orthopaedic surgery and the lives of patients crippled by articular diseases. However, these and other implanted medical devices sometimes induced their own often distinctive histopathological reactions.<sup>5</sup> Histopathologists clearly have an important role in identifying iatrogenic disease, but this requires vigilance and knowledge of current developments in medicine and surgery. The specialty cannot be practised in isolation.

Advances in fibreoptics<sup>6</sup> led to flexible and longer endoscopes, often superseding their rigid precursors of limited anatomical reach. In colonoscopy, for example, a rigid instrument could reach, with biopsy if indicated, often no further than the sigmoid colon. From the 1960s onwards, progressive improvements in fibreoptic flexible instruments yielded a considerable increase in the number of biopsies from each examination. Whereas biopsies through rigid endoscopes were relatively large and few, those from flexible endoscopies usually became smaller and more numerous. Unfortunately, smaller biopsies have not lessened clinical expectations of the reliability and diagnostic precision of the histopathologist's report.

Fifty years ago, some may have predicted the decline of diagnostic histopathology, believing that it would be displaced by the growing sophistication of medical imaging, by the discovery of new biochemical markers of disease, and, however implausibly, by

sheer clinical acumen. On the contrary, histopathology workloads increased massively. For example, in the period 1954–2004 there was an eight-fold increase at the Gloucestershire Royal Hospital.<sup>7</sup>

This inexorable rise in histopathology workloads, especially at a time when many consultant posts in the UK remained unfilled, prompted the Royal College of Pathologists to publish professional guidance on identifying histopathology requests and specimens of limited or no clinical value.<sup>8</sup> An evidence-based approach identified clinical samples that made little or no contribution to patient care, either because biopsy had been superseded by a more informative non-invasive procedure, or because the result was unlikely to influence the patient's treatment. One department estimated that 30% of oesophageal biopsies and >60% of gastric biopsies that it received were of little or no clinical value.<sup>9</sup> If this guidance were put into practice, a significant reduction in workload would result.

Other elements of the histopathology workload declined, but sometimes by substitution. Frozen sections for intraoperative diagnosis of breast lesions were commonplace until the 1980s, but were supplanted by outpatient procedures such as fine-needle aspiration cytology or now, more commonly, core biopsy.

Postmortem examinations have all but vanished, except when determination of the cause of death is required by law. This decline has often been attributed to public concerns about organ retention prevalent in the UK in the late 1990s, but it long pre-dates that episode, and is attributable more to clinical disinterest.<sup>10</sup> The reliability of postmortem imaging, as an alternative to dissection, is now the subject of much research.<sup>11</sup> It is not inconceivable that the decline in postmortem examinations, including histology and storage of tissue samples for review, could result in delayed recognition of some new hazards of modern medicine.

## Advances in understanding disease

'Of all the clinical disciplines, pathology is the one that most directly reflects the demystification of the human body that has made medicine so effective and so humane.'<sup>12</sup>

In the early 1960s, only four types of lymphoma were recognized—lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma, and Hodgkin's disease—but these categories were soon found to be insufficient to account for the range of clinical

behaviour shown by histologically similar lesions. Many new and seemingly rival lymphoma classifications emerged in the ensuing decades, all derived from a greater understanding of the cells populating the lymphoid system. Some histopathologists may have been bewildered (a distinguished haematologist even resorted to parody)<sup>13</sup> by the plethora of new classifications and diagnostic criteria for these lesions,<sup>14</sup> but the greater precision of lymphoma diagnoses has undoubtedly contributed to much more effective treatment and significantly prolonged survival.

A key factor in advancing knowledge of lymphoma subtypes, and indeed of many other disorders, was the development of the immunoperoxidase<sup>15</sup> and similar immunohistochemical techniques, accompanied subsequently by exquisitely specific monoclonal antibodies.<sup>16</sup> This was a paradigm shift in histopathology, enabling cellular phenotypes to be identified from their molecular signatures. These technical developments were accompanied by a correspondingly sharp fall in the use of electron microscopy for tumour diagnosis.<sup>17</sup>

Breast cancer exemplifies well the progressive refinement of histopathological diagnosis. In the 1960s, the grading scheme of Bloom and Richardson became generally accepted for assigning invasive breast carcinomas to different prognostic categories according to the degree of differentiation.<sup>18</sup> Unacceptable levels of reproducibility and consistency led Elston and Ellis to make the grading criteria more objective by semiquantitatively evaluating tubule formation, nuclear pleomorphism, and mitotic count; this achieved a much stronger correlation with prognosis.<sup>19</sup> The refined grading scheme further improved the power of the Nottingham Prognostic Index, which integrated tumour grade with two elements of tumour stage—tumour size and lymph node involvement.<sup>20</sup> Recently, progress towards more individualized clinical decisions has come from the inclusion of biomarkers to form the Nottingham Prognostic Index Plus.<sup>21</sup>

Molecular pathology has transformed (or has the potential to transform) the tissue-based diagnosis of some neoplasms. In addition to detecting the molecular hallmark of a tumour type (e.g. the fusion gene product resulting from t(X:18) in synovial sarcoma), a tumour's gene expression profile may predict, more powerfully than can histological criteria, a favourable prognosis<sup>22</sup> or, conversely, therapy failure.<sup>23</sup> Purely descriptive diagnoses based solely on morphology, such as small blue round-cell tumour, may well give way to a molecular taxonomy.<sup>24</sup>

In addition to the diagnosis and, where possible, grade, the histopathologist's report of tumour biopsies often includes assessment of predictive markers forecasting the likely response to targeted therapy; for example, in breast cancer biopsies, steroid receptor and HER2 status. However, countless prognostic and predictive markers reported in pathology journals have failed to be adopted in clinical practice. All too often, these studies have been performed with insufficient regard to sample size, statistical rigour, and experimental design. In their critical appraisal of cancer prognosis studies, Hall and Going highlighted the deficiencies and limitations of many of these investigations. They proposed a more robust approach comprising, in sequence, assay definition, retrospective testing, and prospective testing, ideally as part of a clinical trial.<sup>25</sup>

Since the mid-20th century, histopathologist's reports have grown considerably in length and information content.<sup>26</sup> Formerly, reports of tumour resections were often limited to confirmation of the diagnosis and, by modern standards, rudimentary information about grade and stage. The evidence-based introduction of new and invariably more complex grading and staging, together with meticulous assessment of resection margins, compelled histopathologists to devise better ways of recording and conveying this information. Audits had revealed that clinically important data, capable of influencing treatment and survival, were often omitted from histopathological reports.<sup>27</sup> Template proformas proved to be the best way of ensuring the most complete reporting of these datasets;<sup>28</sup> these proformas have now been widely adopted.

## Professionalism in histopathology

'We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing.'<sup>29</sup>

Professionalism underpins the trust that patients have in those who contribute to their care. The greatest need for professionalism in histopathology is often when dealing with doubt, uncertainty, and diagnostic disagreements.

The 'tissue diagnosis' continues to have considerable weight in clinical decisions affecting the treatment of patients. Problems commonly arise with

intrinsically doubtful lesions, such as proliferative lesions that seem to lie on a morphological continuum. Lesions at one end of the apparent continuum are unequivocally benign, whereas those at the other extreme are malignant or, if *in situ*, at least have the potential to invade. Lesions of uncertain behaviour constitute a nosological conundrum: at which point on the continuum should words such as 'malignant' or 'carcinoma' be applied? The binary benign-versus-malignant paradigm was gradually challenged in the 20th century, partly because apparently intermediate and ultimately indeterminate lesions were often picked up in screening programmes, notably for breast cancer. In 1995, Elliott Foucar questioned whether the terminology for such lesions could remain safely in the hands of pathologists—'The pathology monopoly on nosology has become dysfunctional. Pathologists' inability to move beyond their benign vs malignant paradigm should result in loss of their terminology monopoly.'<sup>30</sup> Fortunately, histopathologists have not been deprived of their leading, but collaborative, role in disease classification and nomenclature, exemplified by the authoritative series of 'Blue Books' comprising the World Health Organization/International Agency for Research on Cancer Classification of Tumours, a project established in 1956.

Despite a wealth of research, some neoplastic lesions continue to be frustratingly difficult to categorize reliably in a prognostically meaningful way. Formerly, there may have been a tendency to be as decisive as possible (either benign or malignant), and only later for an erroneously benign diagnosis to require correction when metastases appeared or vice versa. Now it is widely accepted that some lesions of dubious behaviour are best labelled 'as 'borderline' or having 'uncertain malignant potential'. In fact, as long ago as 1929, such entities were labelled 'semi-malignant'.<sup>31</sup> Codifying uncertainty in this way highlights a continuing need for further work to improve the clinical predictiveness of histopathological diagnoses.

To improve diagnostic consistency, a major professional development in recent decades was the introduction of external quality assessment (EQA) schemes. Technical and analytical EQA in other pathology specialties was introduced with comparatively little difficulty, because, first, the results being compared between laboratories were usually numerical, and second, deviant results were likely to be attributed to a reagent or machine. In contrast, histopathological EQA schemes were initially difficult to initiate and organize, because the results being

compared were interpretive diagnoses, and outlier opinions would be attributed to an individual.<sup>32</sup> Nevertheless, participation in EQA aligned to the scope of a histopathologist's practice is now firmly established, including the procedures for dealing with persistently poor performance.

Subspecialization in histopathology has become increasingly common in recent decades. Although many patients are unaware of the histopathologist's role in their care, from their perspective the histopathologists' experience and expertise, and therefore their specific diagnostic competence, is vital. This is far removed from the situation in the 1960s in the UK and elsewhere: other than in teaching hospitals, the pathology service was often the responsibility of a single general pathologist.<sup>33</sup>

Credentialing subspecialty expertise in many medical and surgical specialties usually occurs on certified completion of training. In contrast, in the UK, other than for neuropathology, forensic pathology, and paediatric pathology, subspecialty competence in histopathology is more loosely recognized. Some weight must be given to participation in continuing professional development and EQA aligned with the individual's diagnostic repertoire. The individual's workload must also be sufficiently large to be reliably audited and to ensure familiarity with the range of problems likely to be encountered, but not so burdensome that difficult cases receive insufficient attention.

Misdiagnosis in histopathology is professionally challenging. First, particularly with neoplasms, the management of the patient often hinges on the histopathologist's opinion of a biopsy. Consequently, a misdiagnosis can be clinically catastrophic. Second, the material on which histopathologists give opinions is archived, and therefore readily available for review. A histopathologist responsible for a misdiagnosis cannot argue that the biopsy was in a different form when originally reported. Third, unless there is an indisputable pathognomonic feature, the diagnosis is the histopathologist's interpretive opinion, and not a matter of fact.

A significant and somewhat burdensome professional development has been active (often mandatory) involvement in multidisciplinary teams. Histopathological diagnoses in cases of presumed or suspected malignancy are frequently considered alongside clinical and radiological findings in meetings of multidisciplinary teams.<sup>34</sup> Preparation for these meetings, typically necessitating review of biopsy and resection histology, is time-consuming and has added significantly to overall workloads.<sup>35</sup> Although, intuitively, multidisciplinary working in cancer care should

improve clinical outcomes, the evidence for effectiveness is currently scarce.<sup>36</sup>

## Conclusions

‘The art of medicine consists of amusing the patient while nature cures the disease.’<sup>37</sup>

If Voltaire’s *bon mot* about 18th-century medicine had any credence, it reflected the therapeutic impotence of our predecessors. The transformation of medicine in the ensuing centuries was driven largely by pathology. Pathology upgraded medicine from just a caring profession to a curing profession. Twenty-first-century medicine is patient-centred and evidence-based, with much of the evidence being rooted in our greater understanding of disease through advances in pathology.

The specialty’s origins were in morbid anatomy, mainly autopsies. Microscopy, which became emblematic of the specialty, enabled diagnosis and prognosis with much greater precision and reliability. Techniques such as immunohistochemistry and in-situ hybridization allowed molecules that were not detectable with tinctorial methods to be visualized microscopically. Now, the face of histopathology is changing: there is more than meets the eye—molecular pathology.

Therefore, although the tissue diagnosis is still dominant, the question arises of whether its basis in morphology is likely to weaken in an era of molecular medicine. The application of molecular genetic analyses to tumour diagnosis has even led some to question whether microscopy will survive.<sup>38,39</sup> Others, rightly in my opinion, have staunchly defended the durability of microscopy in diagnostic pathology, not from loyal adherence to a traditional way of working, but because of the range and depth of information yielded even by a haematoxylin and eosin (H&E) stained section.<sup>40,41</sup> Rosai’s argument for the continuing role of morphology, particularly in diagnosing neoplasia, is compelling—‘After all, the morphologic appearance of a tumour as seen in an H&E slide represents the grand synthesis of thousands of genes working in concert and sometimes in opposition, and there is probably not a single gene that plays an important role in the neoplastic process whose expression is not manifested in one way or another in a morphologic change that can be detected by those with the training and ability to do it.’<sup>42</sup>

Whether microscopic morphology or molecular pathology should predominate is a spurious argument—the quest ... for the diagnostic “gold standard” is intrinsically flawed and sets up an

inappropriate and pointless conflict ... inconsistent with the real practice of pathology’.<sup>43</sup>

In his provocatively titled *The end of surgical pathology*, Heffner warned of the ‘end of development or progress of surgical pathology’.<sup>44</sup> Has histopathology run its course? Is it now just a matter of applying the knowledge accumulated thus far, while the battle against disease advances on a new frontier—molecular pathology? In an era of stratified and personalized medicine, is the role of morphological histopathology now rather limited?<sup>45</sup> Crucially, as molecular profiling of tumours proves beneficial to patients, should the results separately influence clinical decisions, or should they be blended with morphology as an integral part of the histopathologist’s repertoire and responsibility?<sup>46</sup>

In 2017, we are not witnessing the end of histopathology or even the beginning of its end, but we could be at the end of the specialty’s beginning.

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