14 The Changing Work Patterns of Pathology

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INTRODUCTION

The history of British pathology can be traced back to the 18th century when the best clinicians, such as the Hunter brothers, William and John, began to perform autopsies on their patients and to collect their autopsy and biopsy specimens into museums. The first half of the 19th century saw the introduction of microscopy and the setting up of laboratories, staffed initially by part-time clinicians. Later in the century some full-time appointments were made and Chairs of Pathology were established in major cities; most were in morbid anatomy, with some in bacteriology. However, in comparison with Continental Europe, the recognition of clinical pathology (which included diagnostic histopathology) as an independent discipline in the UK was delayed until the second decade of the 20th century. Furthermore, although Pathology Departments were present in most Medical Schools, there were very few in non-teaching hospitals (Cunningham, 1992). Pathology tests were, therefore, available to only a very small number of privileged patients. Today, 100 years on, all clinicians and their patients have access to high-quality diagnostic histopathology services, including the latest molecular and genetic techniques. It is pertinent to this celebration of the centenary of The Pathological Society that this review gives an account of the profound changes that have taken place in the provision of these services and their impact on workload in diagnostic histopathology. For balance we have divided the century into two 50-year periods, 1906–1956 and 1957–2006.

THE FIRST 50 YEARS (1906–1956)

Background

Before the question of workload patterns can be discussed it is important to describe the nature of Pathology Services in this period. Pathology in Medical Schools was based in Departments of Morbid Anatomy, which were mainly concerned with teaching medical students (largely from autopsies) and carrying out basic pathophysiological research. However, in the early period after the First World War many had little involvement in patient care and some influential academics, such as Boycott at University College, London, even believed that the carrying out of 'blood tests' was more the preserve of clinicians than pathologists (Cunningham, 1992). Bacteriology was established as a discipline in its own right but the emerging field of clinical pathology, encompassing histopathology, chemical pathology, haematology and immunology, was in its infancy and many of the duties that are now accepted as the preserve of pathologists were carried out by clinicians. The next 20 or 30 years saw the gradual establishment of Pathology Departments in the larger District General Hospitals. These were usually general departments covering all disciplines and headed by a single-handed pathologist whose main interest was morbid anatomy and histology. According

to Cunningham (1992), the proper pattern for a modern Pathology Department was established in 1934 by Kettle at the newly founded British Postgraduate Medical School at the Hammersmith Hospital, London. He divided his department into sections that operated independently under a sub-departmental head, covering morbid anatomy, bacteriology, chemical patho-logy and haematology. During the Second World War clinical pathology developed more rapidly, largely under the auspices of the Emergency Medical Service. Under this scheme the establishment of laboratories in London and throughout the provinces formed the basis of the pathological services that came into being when the National Health Service was introduced in 1948.

Workload

It is difficult at this distance to give an accurate account of the typical workload of a pathologist in those early days. Apart from overseeing the technical aspects of all the disciplines, he or she would have had a substantial autopsy practice, including work for HM Coroner, although many of the latter cases were being performed by general practitioners and even hospital-based clinicians. Diagnostic (or surgical) pathology usually occupied less time and the majority of specimens were derived from major surgical procedures such as gastrectomy, colectomy, hysterectomy and mastectomy; the main purpose of histological examination of these specimens was simply to confirm the clinical diagnosis. Biopsy specimens would have been restricted to easily accessible sites such as skin, endometrial curettings and those to which a rigid 'scope' could be applied, such as recto-sigmoid, larynx, oesophagus and bronchi. Liver biopsies could only be obtained during procedures such as exploratory laparotomy and were nearly always performed to investigate discrete lesions found incidentally at this time, rather than as part of a general diagnostic work-up.

In most cases diagnosis was based on examination of a small number of blocks from the specimens, stained with conventional haematoxylin and eosin (H&E). Special stains such as van Gieson, periodic acid–Schiff and Congo Red were used sparingly. Histopathology reports were largely descriptive and contained little prognostic or predictive information.

There was little or no direct involvement in patient management and no concept of multidisciplinary team working. Perhaps the closest that the pathologist came to participation in the decision-making process was in the performance of intra-operative frozen sections. Despite the fact that the freezing microtome was introduced in the latter part of the 19th century and was advocated for examination of tissues at operation (Senn, 1895; Gal, 2001), it was not until 1905 that it became accepted as a routine procedure (Wilson, 1905). According to Haagensen (1986) this technique was first suggested for breast disease by the gynaecologist Thomas Cullen at Johns Hopkins, Baltimore, USA in 1900. At this time Halsted, the renowned breast surgeon, was still dependent on clinical diagnosis alone to select patients for radical mastectomy and about 10% were operated on unnecessarily for benign disease. One of Halsted's assistants, Bloodgood, learnt how to perform frozen sections and solved the problem (Bloodgood, 1914). The equipment was rather basic and it was not possible to produce thin sections of the quality obtained by a modern cryostat; nevertheless, by 1938 Breuer reported an overall accuracy of 88.9%, with no false-positive results, although in general the false-positive rate was about 1–2% (Breuer, 1938). Frozen sections were carried out most frequently on samples from breast (30%), lymph node (15%), gastrointestinal tract (10%) and lung/thorax (10%). In most cases the procedure was carried out to confirm a clinical diagnosis of malignancy before proceeding to therapeutic surgery, whereas in others an unexpected mass or nodule might be sampled to exclude metastatic disease.

We noted above that, in some general hospitals, pathology testing was carried out by clinicians. This usually applied to autopsies and such 'blood tests' as were available, but in some hospitals clinicians also ran Diagnostic Histopathology Departments. For example, at St Bartholomew's Hospital, London, it was traditional for the gynaecologists to report on their own specimens and this practice even continued until the 1970s. The same can be said for dermatopathology. Even

today many clinical dermatologists are expert histopathologists, particularly in the assessment of inflammatory diseases of the skin.

THE SECOND 50 YEARS (1957–2006)

Background

In general the practice of diagnostic histopathology differed little in the first decade of this period from the previous 20 or 30 years. There was still a relatively large autopsy workload, the case mix in diagnostic histopathology was unaltered and intra-operative frozen section was practised widely as a precursor to major surgery. Indeed, the basic technology of histopathology has not changed significantly during the whole of the century since the foundation of The Pathological Society. The majority of specimens are still fixed in formalin and embedded in paraffin wax, sections are still cut on microtomes, H&E is the routine first-line stain and light microscopy is the main means of arriving at a diagnosis.

In 1963, when one of us (C.W.E) was about to embark on his career in histopathology, it was perceived as outmoded and only marginally relevant to patient management; some predicted that the discipline would disappear altogether, to be replaced by more sophisticated techniques such as the automated multichannel analysers being developed in clinical chemistry laboratories. How wrong the doubters were can be seen very simply in the steady and significant rise in overall workload in this second 50-year period in one District General Hospital, which can be regarded as representative for the whole discipline (Fig. 14.1). Yet few, if any, could have envisaged the profound changes that would occur in our discipline in the last 40 years, greater than at any time in the history of histopathology. This renaissance has been due to a number of different but interconnected factors, but the key to its continuing importance, even in the modern 'molecular' age, is the imperative to establish an accurate tissue diagnosis before treatment is started. Most of the factors

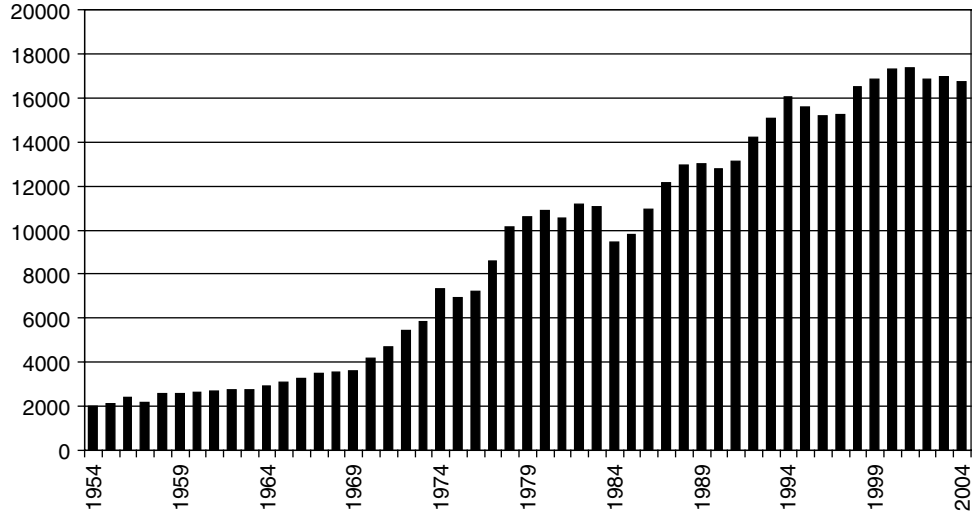

Figure 14.1 Cumulative histopathology workload figures for the 50-year period 1954–2004 at the Gloucestershire Royal Hospital. Although demonstrating a relatively consistent rise, there are two notable dips. The first, in 1984–1985, is an artefact because of a change in the way the specimens were counted. The second, in 1995–1996, was the result of the pathologists' proactivity, with the prohibition of routine antral biopsies for the diagnosis of helicobacter infection.

that have driven the changes in our discipline are clinically related and due to improvements in our understanding and treatment of the major diseases, such as cancer, whereas some, such as the development of immunohistochemistry (Taylor and Kledzik, 1981; Gatter, 1989), are intrinsic to the discipline itself. There are two broad clinical areas in which histopathology has become increasingly influential: pre- or non-operative diagnosis; and prognostication and prediction of disease outcomes. We will discuss the general implications of these changes but in order to illustrate their impact on workload patterns we will give examples from our own sub-specialties.

Pre- or Non-operative Diagnosis

General considerations

There have been huge improvements in biopsy techniques in the last 50 years. A major advance was the introduction of percutaneous needle biopsy, which enabled the investigation of solid internal organs not previously accessible without exploratory surgery. The first such needle, the Vim-Silverman, was initially introduced to improve the preoperative diagnosis of cancers (Silverman, 1938) but was also used for liver biopsy. A similar needle was devised for renal biopsy by Iversen and Brun (1951). The Vim-Silverman needle was subsequently superseded by the Menghini needle (Menghini, 1958), which was safer and easier to use than the Vim-Silverman, produced sufficient tissue to support techniques such as histochemistry in addition to light microscopy and gave less crush artefact. Following its success in liver biopsy (see also below), the Menghini needle was subsequently applied to other areas such as renal, prostate and lung biopsy. Even greater improvements were heralded by the development of disposable needle-core-cutting devices such as the 'Tru-Cut' needle (Rake *et al*., 1969; Vitums, 1972) and, more recently, automated spring-loaded biopsy guns (e.g. the Bard Magnum and the Manan Pro-mag). Allied to high-resolution ultrasound guidance and, where necessary, 'long throw' needles, most organs in the body, including paraaortic or mediastinal lymph nodes, are now accessible to needle biopsy. The other major advance has been the invention of flexible fibre-optic endoscopic devices in the early 1970s (Kirsner, 1998; Cotton and Williams, 2003), which are not only much safer than rigid endoscopes but permit far more extensive sampling, especially in the gastrointestinal tract (see below).

In parallel with these improvements in biopsy technique, conventional light microscopy has been complemented by refinements in ancillary diagnostic methods: histochemistry, which retains considerable importance in the evaluation of liver, renal and gastrointestinal biopsies; electron microscopy, which is a central component of renal biopsy assessment; and immunohistology, which has revolutionised the accuracy of differential diagnosis in tumour pathology.

These developments have, of course, contributed to the steady and significant rise in workload referred to above; for example, at the Nottingham City Hospital biopsy specimens have nearly doubled in the last 10 years and now account for 40% of the overall workload (Table 14.1). They have also led to the establishment of pre-non-operative Multidisciplinary Team Meetings (MDTM), which is another significant call on a pathologist's time. There is a general consensus that team-working in cancer management is good for the patient and in particular should lead to consistency of therapeutic approaches with, it is hoped, enhanced quality of care. What is less

Table 14.1 Comparison of biopsy and resection specimens at Nottingham City Hospital in 1994–1995 and 2004–2005

Year	Biopsies	Resection	Total	Biopsy percentage
94/95	4306	13 508	17 814	24%
04/05	7749	12 296	20 045	40%

clear is whether the MDTMs are a cost-effective way of achieving such team-working. There was a very lively debate about this at the Summer 2005 Newcastle Pathology Meeting.

Breast disease

Although fine-needle aspiration cytology (FNAC) became popular throughout Europe as an alternative to frozen section in the diagnosis of breast lesions (Franzen and Zajiceck, 1968), it was used only sparingly in the UK. Instead, a variety of needles that produced a histological sample were developed, the most successful of which was the manual 'Tru-Cut' (Roberts *et al*., 1975; Elston *et al*., 1978). Use of this technique enabled a definite preoperative diagnosis of carcinoma in 75% of cases. This resulted in a substantial reduction in the number of 'open-ended' frozen sections, many of which, it should be noted, revealed benign disease only. Operation lists became more efficient and there was more productive use of pathologist's time. 'Tru-Cut' biopsy was less successful in the diagnosis of benign lesions; for example, a definite diagnosis was only possible in 50% of fibroadenomas. Nevertheless, a significant reduction in unnecessary excision biopsies for benign disease was achieved.

About a decade later the introduction of mammography as both a diagnostic and a screening procedure led to the need to sample smaller palpable and impalpable lesions. More precise targeting was provided by high-resolution ultrasound guidance. Paradoxically, the 'Tru-Cut' needle was unsuitable in this setting, for technical reasons, and this led to a resurgence in interest in FNAC.

In many centres, for the next 10–15 years FNAC was the main diagnostic technique, so that in the Nottingham City Hospital, for example, the annual total of breast FNAC specimens rose to approximately 2500. The Standard of Care for the pre- or non-operative assessment of breast lesions became the Triple Approach, based on clinical examination, imaging (mammography and/or ultrasound) and FNAC (Dixon *et al*., 1984; Hermansen *et al*., 1987). The preoperative diagnosis rate for invasive carcinoma was approximately 90%, but that for ductal carcinoma *in situ* (DCIS) was only 75–80% due to the difficulty in obtaining representative samples from small areas of mammographically suspicious microcalcifications. This problem was solved in the 1990s by the introduction of automated spring-loaded needle core biopsy (NCB) and more recently vacuum-assisted mammotomy (VAM). These developments eventually led to the replacement of FNAC by NCB in most UK breast units. Audit for the Nottingham Breast Screening Service shows that even for screen-detected breast carcinoma a preoperative diagnosis rate of close to 100% can be achieved (Table 14.2). Definite positive diagnosis of benign lesions such as fibroadenomas is also possible in the majority of cases, thus reducing the need for excision biopsy. This approach has resulted in an annual workload of, on average, 2000 NCBs, about a third of which require multiple levels for the assessment of microcalcifications or suspicious epithelial proliferations (11 109 biopsies January 2000–November 2005).

The use of immunohistology in NCB has increased dramatically in the last 10–15 years for both diagnostic and therapeutic reasons. Diagnostically, for example, the use of a panel of epithelial immunostains can differentiate an infiltrate of carcinoma cells from an inflammatory process, or a metaplastic spindle cell carcinoma from a soft-tissue sarcoma. In terms of therapy there is an

Table 14.2 Audit of preoperative diagnosis of carcinomas in the Nottingham Breast Screening Service, 2003–2004

Type	Number of cases	Preoperative diagnosis
Invasive	156	156 (100%)
Ductal carcinoma *in situ*	34	33 (97%)
Total	190	189 (99.5%)

Table 14.3 Reporting categories for needle core biopsy of breast, recommended by the National Coordinating Committee for Breast Pathology

B1 – Unsatisfactory/normal tissue only
B2 – Benign
B3 – Uncertain malignant potential
B4 – Suspicious
B5 – Malignant

increasing demand from clinicians for assessment of hormone receptor status (aestrogen receptor and progesterone receptor) on core biopsy, particularly in elderly patients or those with locally advanced disease in whom primary hormone therapy is contemplated.

A further development in many Breast Units has been the introduction of synoptic rather than narrative reporting, based on the B1–B5 system (Table 14.3) recommended in the National Health Service Breast Screening Programme (Non-operative Diagnosis Subgroup of the National Co-ordinating Committee for Breast Pathology, 2005); this saves both pathologist and secretarial time, especially if applied electronically.

Liver disease

As noted above, the introduction of the Menghini needle helped put liver biopsy interpretation 'on the map'. This procedure provided tissue of sufficient quality to support light microscopic, histochemical and even ultrastructural studies. Newer core biopsy devices such as the 'Tru-Cut' biopsy and biopsy guns have refined the technique; this includes coating the needles with synthetic materials thought to contribute to better quality histology with reduced artefact (Fukuda and Inokuti, 2004). For most conditions percutaneous biopsy yields a satisfactory specimen. Ultrasound guidance can be particularly helpful in dealing with small focal lesions but is also increasingly applied to obtain samples in patients with diffuse disease. The development of biopsy via the transjugular approach has been particularly helpful in providing specimens from patients who are more unwell, e.g. those who have a bleeding diathesis or marked ascites (McAfee *et al*., 1992). In many centres such specimens are now almost as impressive as those taken percutaneously using ultrasound.

In the early days liver biopsy was used primarily in the investigation of obstructive jaundice and suspected infections (including, in some parts of the world, diagnosis of disorders such as schistosomiasis). Biopsies are now much less commonly seen from patients with biliary obstruction because imaging procedures have improved and complications of biopsy are recognised to be greater in patients with obstruction than in other situations. The general approach to liver biopsy interpretation has not altered radically since the mid-1950s/early 1960s. For the majority of cases, routine H&E-stained sections together with a panel of simple histochemical stains is sufficient for a full histopathological diagnosis.

Immunohistochemistry has, arguably, played a lesser role in hepatopathology compared to many other areas, although it is of particular help in defining the nature of malignant tumours (primary versus secondary; hepatocellular versus cholangiocarcinoma). There are a number of commercially available reagents that can identify infective agents but much of the important clinical information in relation to hepatitis B and hepatitis C, for example, can best be obtained from serological/virological analysis. There is a growing interest in the application of proteomics and genomics on liver biopsy material but this remains an adjunct and is currently best regarded as being within the research domain rather than applied practice.

It is worth remembering that the procedure of liver biopsy carries a not insignificant morbidity and even mortality. Deaths from biopsies are said to occur in between 1 in 1000 to 1 in 10 000

examinations; the procedure is therefore not to be undertaken lightly. A number of centres have sought to develop FNAC as an alternative to needle biopsy. Although there is little doubt that this can be a safe and effective approach in the diagnosis of mass lesions, it is not of any value in the investigation of common necro-inflammatory conditions or in the monitoring of post-transplant complications.

Throughout the latter half of the 20th century there was a continued rise in the use of liver biopsy; this was probably contributed to by the development of clinical hepatology as a distinct sub-specialty. There was an almost exponential rise in the number of biopsies undertaken following the identification of hepatitis C as an important human pathogen. Even the earliest studies of this very common condition showed that investigation of liver function tests did not provide any indication of the severity of the disease; as discussed below, liver biopsy interpretation has remained a cornerstone for assessing patients for therapy in this condition. The other stimulus for an increase in liver biopsy numbers, at least in the larger centres, has been the development of liver transplantation. Again, it became clear that clinicians could not rely on the common 'liver function tests' to monitor how the liver was faring postoperatively and in particular whether there was any rejection (Sebach and Samuel, 2004).

Since the late 1990s many departments, including the large tertiary centres with supra-regional liver units, have seen a plateau in the number of liver biopsy requests. In the transplant units there has been a decline in the interest and justification of protocol biopsies (in the past many patients would have an annual 'MOT' biopsy). Clinical algorithms have been drawn up for certain conditions that have obviated the need for biopsy diagnosis; clearly this is driven by the morbidity and even mortality referred to above. Such algorithms are not without their problems and frequently overlook the fact that the liver often harbours more than one pathological process! Biopsies are still regarded as the 'gold standard' for assessing the degree of fibrosis (see below) but a number of international groups have sought to identify surrogate markers that would again overcome the need for biopsy (Rosenberg *et al*., 2004); although these are exciting developments they are yet an unproven clinical utility (Afdhal, 2004). Thus, we may see a slight decline in liver biopsy requests over the next decade or so but it is highly likely that this investigation will remain pivotal in clinical hepatology way beyond the retirement date of each of the authors of this chapter.

Gastrointestinal disease

The last 50 years have seen extraordinary changes in the practice of gastroenterology and, thereby, the practice of gastrointestinal pathology. As noted above, undoubtedly the major influence has been the dramatic improvement in endoscopy and the ability to reach areas of the gastrointestinal tract previously only accessible by intra-operative techniques. Flexible upper gastrointestinal endoscopy became more available to most practitioners in this country in the late 1970s and early 1980s. Furthermore, flexible sigmoidoscopy and colonoscopy also wrought dramatic changes in colorectal clinical practice. Not only have these techniques allowed excellent access for pathological diagnosis but they have also dramatically increased our understanding of the pathological processes at play, particularly in the oesophagus and the stomach.

Oesophagus

Although the oesophagus was reasonably accessible by rigid oesophagoscopy, there is no doubt that flexible endoscopy has rapidly increased our knowledge of oesophageal disease. The advent of such endoscopy, particularly with open access, allowing endoscopic and pathological assessment of many patients with reflux-type symptoms, has in part influenced the dramatic increase in the number of cases of Barrett's oesophagus now detected. Although there has been a true increase in the prevalence, the better recognition by clinicians of the disease, particularly the short segment variant, has also led to a significant rise in the number of cases detected histopathologically. At

the same time, our understanding of the diagnosis of reflux disease has also changed pathological practice. It is clear that endoscopic techniques are much better at assessing the presence and degree of reflux-associated disease than pathology. There really can be no indication, now, for routine biopsies of reflux oesophagitis.

Stomach

Flexible endoscopy has greatly increased our knowledge of the pathology of gastritis and peptic ulcer disease. This particularly relates, of course, to Helicobacter infection. Before the discovery of this highly prevalent bacterial infection by the 2005 Nobel Laureates Marshall and Warren (Marshall and Warren, 1983), we had very limited understanding of the pathogenesis of gastritis and peptic ulceration. It rapidly became clear that Helicobacter infection has had a major influence on the epidemiology and pathogenesis of gastric peptic ulceration, duodenal peptic ulceration and on gastric carcinogenesis. Indeed the bacterium is now regarded as a type 1 carcinogen. When all three of us were medical students, we were taught that it was inconceivable that significant bacterial infection could survive the acidic environment of the stomach. We now know that the bacterium is uniquely able to withstand such an acidic environment and, indeed, is the chief cause of gastritis, peptic ulceration and gastric carcinoma in most countries.

Although there is no doubt that Helicobacter infection is the most common significant bacterial infection in the world and that it is so potent in the genesis of gastric cancer, we are seeing evidence of a decreasing prevalence of Helicobacter-associated gastritis, in the UK at least. This is probably mainly related to enhanced socio-economic circumstances. At the same time, the incidence of gastric carcinoma is falling and the disease is now relatively more common in the proximal stomach, compared to the antrum, the most prevalent site in former years. Because of a diminution in Helicobacter infection of the stomach, we have also seen a notable reduction in Helicobacter-associated peptic ulceration in both the stomach and the duodenum. Reactive gastritis, most usually due to drugs, is now the most common type of gastritis demonstrated in endoscopic specimens from the stomach in the UK.

Even in our professional lifetimes, we have been able to see these quite dramatic evolutionary changes, almost entirely related to the epidemiology of Helicobacter infection. There is now good evidence that the age of acquisition of Helicobacter infection, in a population as a whole, is a major determinant of the predominant gastro-duodenal pathological phenotypes in that population (Blaser, 1998). Furthermore, there is tantalizing evidence that the high prevalence of Helicobacter infection in the stomach protects that population from oesophageal disease, most notably reflux oesophagitis, Barrett's oesophagus and adenocarcinoma complicating the latter.

The last 50 years, especially the last 20 years, have seen a dramatic increase in our understanding of gastric pathology, particularly gastritis and peptic ulceration. However, although research by biopsy should of course continue, there is little evidence that the routine biopsy of the stomach, without an endoscopic lesion, can be justified, particularly with the pressure of work that UK pathologists face at this time. For instance, there is little evidence that the additional information provided by histopathological assessment of antral biopsies is of any use to individual patient management; microbiological and serological methodology, for the demonstration of Helicobacter, is now just as effective as histopathological assessment (Howat *et al*., 2006). With the advent of open-access flexible endoscopy, there has been an ever-burgeoning biopsy practice and we would argue that pathologists should resist the routine biopsy. There also needs to be an intensive educational drive by pathologists to ensure that endoscopists understand the indications for histopathological assessment throughout the gastrointestinal tract.

Small bowel

The histopathological diagnosis of coeliac disease has undergone considerable change. Formerly, jejunal biopsy, usually performed by a Crosby capsule, was the method of choice for harvesting

small-intestine mucosa. This technique, using radiological guidance, was prevalent, particularly in children, in the 1970s. Flexible endoscopy has now ensured that endoscopists are easily able to reach the duodenum and biopsies from its second and third parts are now preferred for the accurate diagnosis of coeliac disease. At the other end of the small intestine, colonoscopists reach the terminal ileum in more than 90% of procedures. Indeed, they can regularly intubate the terminal ileum and this allows pathological assessment of terminal ileal disease, particularly, of course, in Crohn's disease. Even newer techniques, such as capsule enteroscopy, are not yet sufficiently developed to allow such capsules to take biopsies but one might envisage that, in the future, biopsies from areas of the small intestine at present wholly inaccessible may be possible.

Colorectum

It is, once again, flexible endoscopy that has dramatically influenced the practice of diagnostic histopathology in colorectal disease in the last few decades. This particularly relates to the assessment and differential diagnosis of chronic inflammatory bowel disease, but open-access colonoscopy has also influenced our understanding of carcinogenesis in the large intestine. Furthermore, colorectal cancer screening will be instituted, in the UK, in 2006 and this will have a major influence on workload patterns in histopathology departments. There are tentative proposals for medical staff to undertake the histopathological assessment of polyps generated from the Colorectal Cancer Screening Programme.

Prognostication and Prediction of Disease Outcome

General considerations

At the beginning of this 50-year period the treatment options for many diseases were relatively limited. In the field of cancer, for example, surgical excision with or without postoperative irradiation was the standard procedure for operable tumours whereas palliative radiotherapy was given in inoperable cases. Cytotoxic therapy was being introduced for the leukaemias and some lymphomas but was not used for solid tumours. The main role of the histopathologist was to confirm the diagnosis of malignancy but there was little input to therapeutic decision-making. Although correlations between histopathological features and prognosis were well established, they were disregarded by clinicians. Gradually, however, new therapeutic regimes emerged as surgical techniques became more precise, radiation therapy better targeted and more effective cytotoxic therapy was developed.

Instead of a standard regime for all those with a particular tumour, it was recognised that patients should be stratified so that each individual receives appropriate therapy. As a result, histopathological assessment has assumed greater importance, specimens are examined more extensively, reports have become more detailed and minimum data sets have been established for all tumour sites. These changes have all contributed to an increased workload not only numerically but particularly in the complexity of the process. Another important consequence has been the inexorable move, especially in large departments, towards sub-specialisation, with pathologists restricting their reporting to one or two organ systems.

Breast disease

Until the last 10–20 years the treatment of all breast lesions, benign or malignant, was predominantly surgical. For invasive breast carcinoma the standard treatment was mastectomy, either simple or radical, with axillary clearance and/or postoperative irradiation to the axilla. Histopathology reports were mainly descriptive and the only prognostic information supplied (or required) was lymph node stage, even in clinical trials of cytotoxic therapy. The resurgence of interest in other prognostic factors began with the demonstration that an index based on a combination of factors (histological grade, lymph node stage and tumour size) gave a more

accurate prediction of survival (Haybittle *et al*., 1982). The relevance to the stratification of patients for adjuvant systemic therapy of such an index is now established, as is its validation in other centres (Clark, 1992; Galea *et al*., 1992; Blamey, 1996; Balslev *et al*., 1994).

Assessment of oestrogen receptor status by immunohistology is now performed routinely on formalin-fixed paraffin-embedded material (Snead *et al*., 1993). Oestrogen receptor status is accepted as a reliable means of predicting response to hormone therapy (Barnes and Millis, 1995) and is part of the minimum data set in most Breast Units. The novel drug trastuzumab, a recombinant humanised monoclonal antibody directed against the epidermal growth factor receptor 2 (HER2), previously used only in advanced cases, has now been shown to be effective as an adjuvant therapy in early breast cancer (Romond *et al*., 2005). Approximately 15% of breast cancers are HER2 positive, but it is envisaged that testing will be carried out on patients in the very near future – a further and expensive addition to the pathology workload. Earlier presentation, partly as a result of mammographic detection, has led to an increasing demand for conservation surgery; approximately 40% of patients now choose this option. This, in turn, has emphasised the need for more thorough pathological assessment of excision specimens and the importance of clear margins (Gage *et al*., 1996).

Although a weak prognostic factor compared with grade, histological type is of importance in our understanding of the biological aspects of breast cancer. For example, the association between the medullary and medullary-like phenotype with BRCA-1 gene mutation carrier status provides interesting insights into genetic and hereditary aspects of the disease (Lakhani *et al*., 1998). The critical role of these and other prognostic factors in patient management has become established in a comparatively short space of time, certainly less than 20 years. They are incorporated in the Royal College of Pathologists histopathology minimum data set and their inclusion in the standard breast histopathology report is now mandatory (Guidelines Working Group of the National Coordinating Committee for Breast Pathology, 2005). Their impact on workload is illustrated by comparing the average number of blocks from a mastectomy specimen ca. 1975 (6–10) with that for a mastectomy (15–20) and wide local excision (25–30) in 2005. Furthermore, in the personal experience of one of us (C.W.E), there is a considerable difference in the time taken to report such resection specimens: an average of 15–20 min in 1975 compared with 45–60 min in 2005. To this must be added the time spent in attending therapeutic MDTMs.

Liver disease

Liver biopsies are used for grading and staging much more in the field of necro-inflammatory disease and for the monitoring of rejection than in neoplastic disease. Although there are grading systems described for hepatocellular carcinoma – the most common malignant liver tumour – overall survival for all grades is pretty appalling and assessment on needle biopsy has not been helpful in prognostication. Indeed, current European protocols have indicated that biopsy of suspected hepatocellular carcinoma should not be performed using any form of needle because of the risk of dissemination of tumour along the needle track (Scholmerich and Schacherer, 2004).

It is principally in the field of viral liver disease in which assessment of severity has been of most value. The various treatment modalities that have been developed for dealing with hepatitis C virus are expensive, associated with significant side-effects and certainly not 100% effective. As a consequence it has been extremely important to develop systems that stratify patients for therapeutic intervention. Over the past 20 years or so there have been a number of scoring systems developed to assess the histological severity of chronic hepatitis.

For many years the most widely used was the Knodell Score, which was developed by Kamal Ishak and colleagues at the Armed Forces Institute of Pathology. In essence this uses numeric scores for a number of different parameters of necro-inflammation and fibrosis, and these are summated to give an overall histological activity index. In the 1990s it became apparent that it

would be important to separate out the assessment of necro-inflammation (grade) from the degree of fibrosis (stage). Furthermore, there is no good biological justification for summating the numeric scores for each of the different assessed features. The modified HAI described by Ishak and colleagues is thus a profile of features, although inevitably many of our clinical colleagues do the summation themselves! Some have argued that we would have been more sensible applying letters rather than numbers to the system, avoiding the misuse of statistics.

Liver pathologists have, however, been concerned with the important issue of sampling (Scheuer, 2003). There are now several well-conducted studies that have demonstrated that unless the biopsy is greater than 2 cm the reliability of grading and staging is substantially reduced. Furthermore, there have been numerous studies looking at inter- and intra-observer variation of such semi-quantitative scores. Some of these have demonstrated a quite appalling lack of consistency, particularly across observers, but, more reassuringly, in individual centres where there has been training of the observers as a group (what Professor Valeer Desmet refers to as 'tuning the violins') the Kappa values are very much better. More recently, similar grading and staging systems have been used increasingly in the assessment of fatty liver disease. In particular they are likely to be applied quite widely to the assessment of non-alcoholic fatty liver disease as new therapies become available to treat this common condition (Brunt *et al*., 2004).

Gastrointestinal disease

Accurate prognostication of cancer started with the meticulous pathological studies of Dukes and his staging system for colorectal cancer (Dukes, 1932; Dukes and Bussey, 1958). In the early 1920s, Dukes first demonstrated that accurate pathological assessment of the spread of colorectal cancer had a profound influence on prognosis. His studies, performed at St Mark's Hospital in London, were based on accurate macroscopic pathological assessment and, in fact, depended relatively little on microscopic assessment. Certainly in the 1970s and 1980s the importance of such macroscopic assessment was somewhat disregarded and we believe that this was a major influence in the overall poor quality of colorectal cancer assessment in pathology departments in the UK (Morson, 1981; Shepherd and Quirke, 1997). Only more recently, with the advent of initiatives by the Royal College of Surgeons and then the Royal College of Pathologists, and the introduction of reporting proformas and minimum data sets, has the quality of colorectal cancer reporting improved in routine pathological practice.

It was perhaps the success of the Dukes classification, which effectively only assesses penetration of the bowel wall and local lymph node involvement, that accounts for the dearth of accurate research on parameters that are now regarded to be of supreme importance in colorectal cancer prognostication. A dramatic change undoubtedly occurred in the early 1980s with the recognition of the importance of surgical complete mesorectal excision (Heald *et al*., 1982; Heald and Ryall, 1986). It was Quirke who championed the importance of pathological assessment of this margin and the influence of margin involvement on local recurrence and prognosis (Quirke *et al*., 1986). Such assessment of margin involvement, and the techniques that accompanied it, is now applied also to colonic cancer and oesophageal cancer.

The same initiatives have occurred in the assessment of oesophageal and gastric cancer. In the last 50 years there has been a dramatic change in the prevalence of these two diseases, with less gastric cancer and much more adenocarcinoma of the oesophagus, the latter related to reflux disease and Barrett's oesophagus. Pathological practice, of course, reflects surgical practice but we have seen a large increase in resections for oesophageal adenocarcinoma and a notable decrease in resections for oesophageal squamous cell carcinoma and gastric adenocarcinoma. The quality of pathological assessment has been improved, particularly in oesophageal cancer resection specimens, with the recognition of the importance of circumferential margin involvement and lymph node involvement.

As with breast cancer, there is no doubt that the accurate assessment of these gastrointestinal cancer resection specimens has had an important influence on the workload of the pathologists. Accurate and diligent assessment of these specimens now takes at least one hour, whereas formerly the macroscopic assessment was often detailed to a junior member of staff or alternatively took a very little time. There has also been the advent of the cancer MDTMs; these have had a significant influence on the pathologist's workload. Most pathologists appreciate the importance of such meetings because they allow accurate analysis of the needs of individual cancer patients in terms of appropriate investigations, surgery, oncological treatment, palliative care and overall prognosis.

SUMMARY

In the last 100 years diagnostic histopathology has developed from a largely passive discipline to one that is proactive and at the forefront of modern patient management. The most dramatic changes have taken place in the last two to three decades due to a combination of improved therapeutic options and well-constructed clinicopathological research. As a result, our discipline has more relevance today than at any time in the past century. The most striking changes have been the growth of pre- and non-operative diagnosis and the provision of factors that are prognostic and predictive of disease outcome. Establishment of a tissue diagnosis is still the 'gold standard' for all cancers and many other diseases. As a result, there has been a steady year-on-year rise both in the overall number of specimens examined and in the complexity of pathology reports.

There is another example where the proactivity of diagnostic pathologists is important. Formerly, the passivity of the specialty was such that pathologists had no influence on which specimens were to be submitted for pathology and thus we accepted all samples sent to us. The first changes occurred nearly 30 years ago when Fox (1978) first argued that the routine examination of placentas from live births was unproductive. Nowadays, most notably in the gastrointestinal tract, pathologists are even more involved in influencing the type of specimens they receive (Fig. 14.1) (Howat *et al*., 2006). Perhaps the best example of this is antral biopsies for the diagnosis of Helicobacter infection. There is no doubt that other much simpler methodologies are easier to perform and cheaper, and we strongly believe that there can be no indication for the routine diagnosis of Helicobacter infection by histopathology. There is an argument that non-malignant disease has lagged behind in developing quality standards utilising minimum data sets, although these do exist in some areas. For both tumour and non-tumour pathology it is essential that we continually assess the evidence base for items that are considered minimum data. This is a stated objective of the Royal College of Pathologists but there are some who believe that at least a proportion of existing minimum data sets contain, from a clinical perspective, redundant information.

It would be injudicious to attempt to predict the long-term future of diagnostic histopathology but in the short to medium term we believe that light microscopy will still retain its importance, complemented by data from evolving molecular and biological techniques.

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