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Clinical Pathology- A Diagnostic Aid?

Professor Stuart Fleming (Professor of Cellular and Molecular Pathology, University of Dundee)
Correspondence to: Prof Stuart Fleming: s.fleming@dundee.ac.uk

ABSTRACT

Clinical pathology is now an essential component of high quality clinical care. Pathology tests are important to reaching a diagnosis in 85% of hospital patients. Indeed in some areas including oncology, infection and transplantation medicine diagnosis and optimum treatment cannot be delivered without histopathological investigation. Pathology testing is a core component of early cancer detection through screening for breast, bowel, cervix and prostate cancers. In the last twenty years pathology has moved from a useful diagnostic aid to a clinical essential.

Introduction

In this article I will argue that Pathology is no longer a useful diagnostic aid but an essential component of high quality clinical care and the practice of evidence based medicine. Indeed through research and clinical trials pathology has often provided the evidence upon which modern patient management is based. The word Pathology was first used in English by Sir Phillip Sidney in his pastoral epic Arcadia (1585). Sidney, like so many Elizabethan courtiers was well educated in the classics, and in his use of 'pathology' he meant the study of suffering and pain (From Greek *pathos*; suffering and *logos;* study). In modern medicine it has tended to have two overlapping meanings; one academic the other clinical. Pathology, as the academic study of disease mechanisms seeking to progress our understanding of disease, is central to evidence based medical practice and the development of new treatments (1). Indeed this continuum from understanding disease to developing new drugs and testing their efficacy has been recognised by the award to Scotland by the MRC of a unique clinical research fellowship programme, the Scottish Clinical Pharmacology and Pathology programme, designed to bring together young pharmacologists and pathologists in joint research efforts. The second sense of pathology is in the use of laboratory methods for diagnosis and patient management. Clinical pathology of this type covers all the main lab disciplines including histopathology, morbid anatomy, haematology, microbiology, clinical biochemistry, immunology and genetics. The importance of these disciplines to modern medicine is emphasised by national healthcare statistics that show that 85% of hospital patients have a diagnosis made on the basis of pathology testing. In the field of histopathology, my own specialty, our major contributions are in the fields of cancer, where virtually every diagnosis depends on pathology, specific infections, inflammatory disease, transplantation and health promotion through screening.

The major skills in histopathology are visual; examining and dissecting abnormal tissue, viewing slides prepared from the tissue on a microscope and adding molecular investigations which allow us to see the expression of protein and RNA in cells. Although the sophistication of microscopy and the addition of molecular methods have greatly improved the accuracy of diagnosis in recent years the principles of histopathology have remained. A skilled histopathologist examining a biopsy under a microscope is simultaneously assessing a large number of phenotypic variables that can account for the disordered physiology giving rise to the signs and symptoms experienced by patients. These visual skills then are to the histopathologist what clinical examination skills are to the GP or physician.

How do these visual assessments contribute to patient management?

Cancer screening programmes are a huge health promotion and disease prevention effort in this country. Pathology practice is an essential component of bowel, breast, cervical and prostate cancer screening (Figure 1). Bowel cancer screening is offered every two years from 50 years of age, the first invitation arrives on the week of your fiftieth birthday! The test is based on the detection of faecal occult blood (Chemical pathology), a positive test leading to an invitation to attend for the second stage of investigation by large bowel endoscopy (2). Lesions seen by the endoscopist are usually biopsied and submitted for pathological examination. These will most often be polyps, often in a pre-malignant phase, which when removed will no longer progress to cancer. However, some of these polyps may show dysplasia and even early malignancy. The UK programme was piloted in Fife, Tayside and Grampian and it became clear during the pilot that pathologists were seeing much earlier colo-rectal cancers than were seen previously from symptomatic patients (3). This was, of course, what was hoped, since these earlier cancers are more likely to be cured, but it has generated challenges to pathologists in their ability confidently to recognise small early cancers reliably. Scottish pathologists have therefore been at the forefront of rolling out the programme across the UK, training other pathology consultants elsewhere in the UK in the diagnosis of early bowel cancer. It is early days but the results of the screening programme are encouraging with many bowel cancers being recognised and treated earlier than previously with the potential to fulfil the aim of reducing bowel cancer mortality.

The anatomy of cancer spread - staging

When a polyp has undergone malignant change the best option for cure is surgical resection. Following surgery, the resected bowel is sent to pathology for investigation. The tissue usually arrives in the pathology department fresh and this enables samples to be taken for genetics and for research. Careful examination, description and dissection of a resected tumour by an experienced pathologist are crucial to many of the treatment decisions for the patient in the post-operative phase of their care. During the 1990s work by a pathologist, Professor Phil Quirke, and his surgical colleagues in Leeds showed that the main factor determining local recurrence and subsequent metastasis of rectal cancer was incomplete resection on the radial meso-rectal margin (4). This work has led to changes in both surgical and pathology practice which has dramatically reduced the frequency of locally recurrent disease (5). The pathologist in his assessment of the resected tumour will make important observations such as the depth of invasion, the presence of lymph node metastases in the mesentery or vascular invasion. These data contribute to tumour staging, measured in all types of cancers, which is a way of assessing the extent of tumour spread and indirectly predicting the likelihood of metastases becoming apparent later. Different staging systems exist for different cancer types however the basic principle is the same for all, staging is an assessment of how far the tumour has spread. The staging systems use measurements of local extent of the tumour (T), the presence of lymph node deposits (N) and distant metastases (M), hence the TNM classification. Perhaps the best-known staging system is that of Dukes staging for colorectal cancer. Whilst this was developed more than 50 years ago and cancer treatment has changed so much it is remarkable that the principles of this classification are still used as a sound guide to prognosis and treatment. The stage of any tumour therefore has a major influence on clinical decision-making about the need for further radiation or medical oncology treatment and is soundly based on good anatomical pathology.

The diagnosis of malignancy

During the dissection the pathologist will also take samples from tumour, adjacent mucosa, other polyps and the excision margins to be processed to slides for microscopic examination by the laboratory scientific staff. The pathologist will then examine the slides to formulate a

diagnosis of the tumour type based on morphological criteria. The pathologist examines the tissue for changes in both the architecture of the tissue and in the cytology, the shape and size of cells and their nuclei. They will also look for evidence of increased proliferation rate, most usually by seeing mitotic figures, evidence of haemorrhage and necrosis and of invasion of the underlying lamina propria. All of these are the cardinal features that identify malignancy in an organ.

The classification of tumours

Within many organs there may be several different types of malignancy. In the lung we have small cell carcinoma, squamous carcinoma, adenocarcinoma, large cell undifferentiated carcinoma and other rarer types. In my own field although we know much about the genetic basis of kidney cancer the classification is based on morphology, albeit with an extremely strong correlation with known genetic changes (6, 7). These diagnoses, based on histology, are crucially important in patient management since the treatment of small cell carcinoma is different from the other types. So the dual diagnostic process of identifying malignancy and then classifying it is an important part of the pathologists work.

The assessment of cancer aggressiveness - grading

In addition to using microscopy to make a diagnosis the pathologist will grade tumours by their histological appearances. Grading systems broadly examine the degree of similarity of a tumour to the tissue from which it has arisen. There are many different grading systems for different tumour types with specific histological criteria used to describe the different grades. For some the cellular differentiation is most important whereas others concentrate on nuclear changes. However, the important thing is that these are all indirect measures of the biological aggressiveness of the tumour.

Molecular changes and therapeutic decisions

Pathologists are key to the identification of important molecular changes that influence management decisions. The best established of these is seen in the pathology of breast cancer. Two types of change are particularly important - hormone receptor expression and Her2 amplification. Nowadays the most reliable way to identify the expression of oestrogen and progesterone receptors is by using immunocytochemistry. In this technique antibodies to the two different hormone receptors are used to stain slides of tumour with the antibody binding then visualised by colour based staining. The intensity of the stain reflects the level of antibody binding and hence the level of receptor expression. Immunocytochemistry allows the pathologist to confirm that it is indeed the tumour cells expressing the receptor and not adjacent normal tissue, a problem which confounded earlier biochemistry testing(8). The pathologist can then score each breast cancer for oestrogen or progesterone receptor expression which will determine the likelihood of response to Tamoxifen treatment. One of the other important alterations in breast cancer is amplification of the Her2 gene leading to overexpression of the Her2 member of the epidermal growth factor receptor family and receptor driven cancer cell survival and proliferation. With the development of a humanised monoclonal antibody targeting Her2, trastuzamab or Herceptin, testing for Her 2 amplification became important. Although initially done using fluorescent *in situ* hybridisation (FISH) directly to visualise the amplified portion of the genome this is now performed using either immunocytochemistry alone or in combination with FISH (9, 10). These tests performed on pathology slides from the tumour are now used to identify those women likely to respond to Herceptin. Furthermore some tumours fail to express any of these markers, so called triple negative breast cancer, and these are managed differently again.

In some tumours molecular testing for oncogenic mutations is used to guide therapy. Lung cancers are frequently driven by overexpression of the epidermal growth factor receptor and are now treated by a humanised monoclonal antibody directed to the receptor. However, the EGFR signalling pathway includes the KiRas oncogene so when mutation of KiRas is also present tumour cell growth is driven preferentially by Ras rather than EGFR. In patients with mutant KiRas bearing tumours EGFR directed treatment is ineffective. Pathologists now routinely test for KiRas mutations in these lung cancers and anti-EGFR treatment is only used for those cases with EGFR overexpression and lacking KiRas mutation (11). Therefore pathology and pathology based molecular analysis beyond traditional histology are now used in critical therapeutic decision making.

Pathology and infection

Although Medical Microbiology emerged as a separate discipline decades ago histopathology contributes significantly to the diagnosis of some infections. When I was a medical student gastritis, peptic ulcer disease and gastric cancer were huge health care problems leading to gastrectomies, vagotomies and patients being treated for years with various drug treatments. That was changed dramatically by one of the most important medical discoveries during my professional life made by a pathologist, a gastroenterologist and a medical student doing a summer vacation project. Helicobacter pylori, a difficult to detect gram negative organism, was found by Barry Marshall and Robin Warren in the stomachs of patients with gastritis and peptic ulcers. They went on to show that it was pathogenic in these situations but also in gastric cancer and lymphoma. Diseases which previously required major surgery with a high morbidity and mortality could now be controlled in most patients by a course of appropriate antimicrobial therapy. For this remarkable work they deservedly won the Nobel Prize for Medicine in 2005 (12). Identification of Helicobacter in gastric biopsies, usually by Giemsa staining, is now an important component of the treatment of patients with upper gastrointestinal symptoms (Figure 2).

In my own field of renal and transplant pathology the histopathological identification of opportunistic infection, particularly by viruses such as CMV and BK virus, in renal transplant biopsy is a frequent problem (13). Since the clinical differential diagnosis is often between rejection or infection this is an important diagnosis to make. The transplant patient experiencing rejection needs to increase his or her immunosuppression but that could be potentially life threatening in the patient with CMV infection. So the demonstration of viral nephropathy by a combination of morphology and immunocytochemistry and its distinction from rejection is an important part of the renal transplant team's care of the kidney recipient.

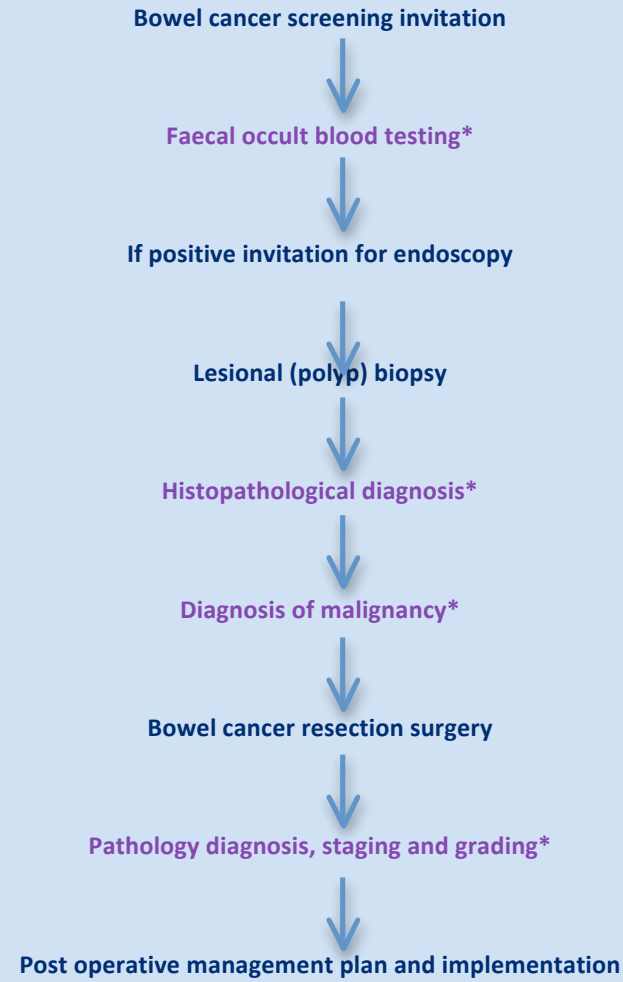
New Diseases

Histopathology has played a key role in identifying new diseases and in dissecting the pathogenesis. The most high profile of these in recent times has been the discovery of a new form of Creutzfeldt Jacob disease (CJD) caused by dietary exposure to the prion responsible for bovine spongiform encephalopathy (BSE). BSE, or as the tabloid press would have it 'mad cow disease', emerged as a significant veterinary health care problem amongst dairy herds in England in the late 1980s. Initially government played down the relevance to human health, but the discovery of variant CJD by James Ironside a neuropathologist, based on unusual histopathological features changed that perception. Ironside showed that this was a new disease, the clinical features were unusual in that it affected younger patients and eventually he, with others, proved the link with the BSE prion (14, 15). Histopathology remains the only robust diagnostic criterion for variant CJD(16, 17). A major public health response was put in place aiming to reduce exposure of the population to potentially

contaminated bovine tissues by exclusion from the food chain. These public health measures have eventually been successful and after a peak incidence early this century variant CJD is now declining in frequency. Hundreds of lives have been saved by the histopathological discovery of new variant CJD and the resulting public health response.

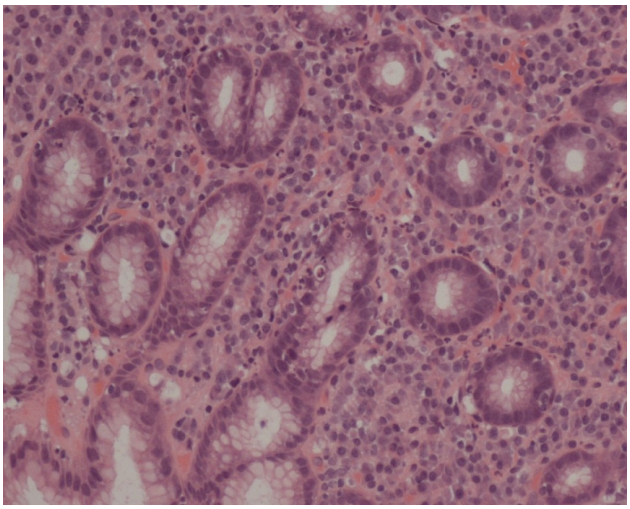
Histopathology is no longer regarded as a diagnostic aid but in many fields, cancer, renal medicine, hepatology, dermatology, neurosurgery and transplantation to name but a few, it is an essential component of patient management. It is incorporated into clinical decision making through multidisciplinary team meetings which are now a standard of care throughout hospital practice. In all health care economic analysis pathology services emerge as one of the most cost effective branches of medicine. Pathology training in Scotland remains at the forefront with four training schools centred on the four clinical medical schools of Aberdeen, Dundee, Edinburgh and Glasgow.

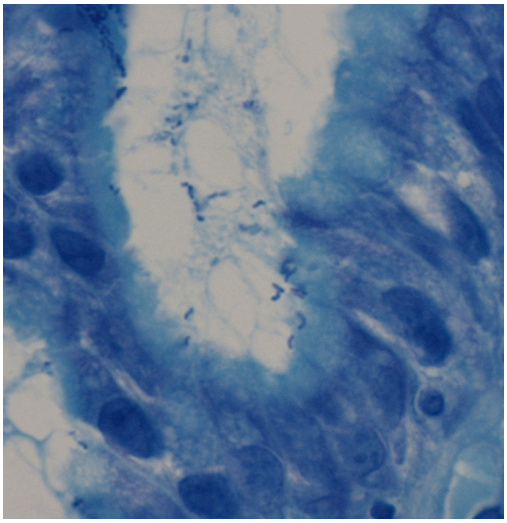
Figure 1. Pathology involvement (*) in bowel cancer screening



This figure highlights that pathology is a fundamental aspect of good clinical management of tumours. It helps guide treatment and aids clinicians discuss prognosis with the patient.

Figure 2. Histopathological examination of a gastric biopsy from a middle aged man with upper abdominal discomfort and pain shows an active chronic gastritis (**LEFT**) H&E X200. The causative Helicobacter organisms are readily seen in a Giemsa stained section of the biopsy - Giemsa X1000 (**RIGHT**).





References

1. Muir RS, Levison DA. Muir's textbook of pathology. 14th ed. / edited by David A. Levison ... [et al.]. ed. London: Hodder Arnold; 2008.
2. Thompson MR, Steele RJ, Atkin WS. Effective screening for bowel cancer: a United kingdom perspective. Dis Colon Rectum. 2006 Jun;49(6):895-908.
3. Steele RJ, McClements PL, Libby G, Black R, Morton C, Birrell J, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. Gut. 2009 Apr;58(4):530-5.
4. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet. 1994 Sep 10;344(8924):707-11.
5. Scott N, Jackson P, al-Jaberi T, Dixon MF, Quirke P, Finan PJ. Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. Br J Surg. 1995 Aug;82(8):1031-3.
6. Fleming S. The impact of genetics on the classification of renal carcinoma. Histopathology. 1993 Jan;22(1):89-92.
7. Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CS, Delahunt B, et al. The Heidelberg classification of renal cell tumours. J Pathol. 1997 Oct;183(2):131-3.
8. Paterson DA, Reid CP, Anderson TJ, Hawkins RA. Assessment of oestrogen receptor content of breast carcinoma by immunohistochemical techniques on fixed and frozen tissue and by biochemical ligand binding assay. J Clin Pathol. 1990 Jan;43(1):46-51.
9. Kay E, O'Grady A, Morgan JM, Wozniak S, Jasani B. Use of tissue microarray for interlaboratory validation of HER2 immunocytochemical and FISH testing. J Clin Pathol. 2004 Nov;57(11):1140-4.
10. Ellis IO, Bartlett J, Dowsett M, Humphreys S, Jasani B, Miller K, et al. Best Practice No 176: Updated recommendations for HER2 testing in the UK. J Clin Pathol. 2004 Mar;57(3):233-7.
11. Langer CJ. Roles of EGFR and KRAS Mutations in the Treatment Of Patients With Non-Small-Cell Lung Cancer. P T. May;36(5):263-79.
12. Pincock S. Nobel Prize winners Robin Warren and Barry Marshall. Lancet. 2005 Oct 22-28;366(9495):1429.
13. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation. May 15;89(9):1057-70.

14. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 1996 Apr 6;347(9006):921-5.
15. Ironside JW. Neuropathological findings in new variant CJD and experimental transmission of BSE. FEMS Immunol Med Microbiol. 1998 Jun;21(2):91-5.
16. Ironside JW, Head MW, Bell JE, McCardle L, Will RG. Laboratory diagnosis of variant Creutzfeldt-Jakob disease. Histopathology. 2000 Jul;37(1):1-9.
17. Will RG, Zeidler M, Stewart GE, Macleod MA, Ironside JW, Cousens SN, et al. Diagnosis of new variant Creutzfeldt-Jakob disease. Ann Neurol. 2000 May;47(5):575-82.