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FIFTEENTH EDITION

MUIR'S TEXTBOOK OF PATHOLOGY

EDITED BY
C. SIMON HERRINGTON

CRC Press
Taylor & Francis Group

MUIR'S TEXTBOOK OF PATHOLOGY

Fifteenth Edition

Edited by

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PREFACE

It is a great privilege to edit this, the Fifteenth Edition of Muir's Textbook of Pathology. Muir's Textbook (or just 'Muir's') was first published in 1924 and has been the stalwart of pathology education for several generations. This Edition is in many ways an update of the Fourteenth Edition, which, as recorded by the Editors in their Preface, differed in a number of ways from previous editions. The structure of the book remains the same and the highly successful case studies and special study topics have been retained, and updated where appropriate. The move to a more integrated approach has been highly successful and the presentation of core knowledge, with development of a more in-depth discussion of specific areas that illustrate recent advances, allows both breadth and depth of coverage. The last Edition saw the involvement of more Editors and authors from outside Glasgow. This trend has continued in this Edition, but many, if not most, of us who did not train or have not worked in Glasgow have been influenced by Glasgow Pathology through use of 'Muir's' during our own training, or our training of others. I hope that this has allowed us to preserve the unique feel of the book.

I am extremely grateful to the other contributors for their efficient and timely engagement with the publishing process. I would also like to thank those who contributed images and other figures: they are acknowledged specifically at the appropriate point in the book. Thanks go also to the publishers, particularly Jo Koster who galvanized the project in the beginning and Julie Bennett who managed the publishing process. Finally, I am particularly indebted to the Editors of the 14th Edition, Professors Levison, Reid, Burt, Harrison and Fleming, for their transformation of 'Muir's' into what it is today; and for allowing the use of their material in this Edition.

C Simon Herrington

2014

PREFACE TO 14TH EDITION

This is the Fourteenth Edition of Muir's Textbook of Pathology, building upon the work of previous editions. It is different in a number of ways from previous editions, but we think it is similar enough to retain the traditional values of its predecessors. We trust we have produced a text that will be useful both to undergraduate medical students and to postgraduates who are interested in having a better understanding of disease upon which to base either their clinical practice or their research, or both.

This edition differs in the balance between general and systematic pathology from most earlier editions, with the general section being relatively shorter. This is deliberate; it is not meant to suggest that we think an understanding of the basic sciences is any less important to clinical practice than it used to be – quite the contrary. What we have tried to do is to focus on the most clinically relevant basic science and we have included some of that in the systematic chapters where its relevance is hopefully easier to appreciate.

We have also introduced into almost every chapter one or two special study topics where the information provided is rather more than most medical educators would include in the core curriculum of a medical undergraduate course. This is intended to interest and stimulate the best students to appreciate that undergraduate education is just the beginning – a window on the exciting and challenging world of disease. We have also included in most chapters, several case histories which illustrate and add to the information provided in the main text, in an attempt to emphasize the fundamental relevance of pathology to clinical medicine. By adopting this format of special study topics and case studies integrated into, but clearly distinguished from, the core text, we are adopting the approach taken to medical education in many medical schools. We strongly support the move in the UK to more integrated teaching of the disciplines in medicine. We, not unexpectedly, believe that the best doctors are knowledgeable about disease processes, and we hope that this belief is reflected in the level at which we have pitched the text.

It will be noted for this edition of the book that for the first time ever the majority of the editors are not based in Glasgow. However, three of us are Glasgow graduates, and we all acknowledge our debt to, and the inspiration we have drawn from, our predecessors in Glasgow Pathology. We are honoured to have had the opportunity to edit this latest edition of 'Muir' and hope that we have done justice to the task.

David A Levison
Robin Reid
Alastair D Burt
David J Harrison
Stewart Fleming

2008

CONTENTS

SECTION 1

CELLULAR AND MOLECULAR MECHANISMS OF DISEASE

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1

APPLICATIONS OF PATHOLOGY

C Simon Herrington

WHAT IS PATHOLOGY?

Pathology is the study of disease. It is central to the whole practice of evidence-based medicine. Arguably, anyone who studies the mechanisms of a disease can be described as a pathologist, but traditionally the term is restricted to those who have a day-to-day involvement in providing a diagnostic service to a hospital or undertake research in a pathology department. Within the discipline there are numerous subspecialities:

- Cellular pathology, including histopathology (the study of tissues) and cytopathology (the branch in which diagnoses are made from the study of separated cells).
- Morbid anatomy is an old term that refers to postmortem dissection, and forensic pathology is the related branch concerned with medicolegal postmortem examinations. These are carried out under the aegis of a legal officer, for example the Coroner in England and Wales, the Procurator Fiscal in Scotland, and the Medical Examiner in the USA.
- Microbiology is the study of infectious diseases and their causes. This can be subdivided into bacteriology, virology, mycology (the study of fungi), and protozoology (the study of infections by protozoa).
- Haematology is the laboratory study of diseases of the blood. This is also a clinical discipline, its practitioners dealing with patients with these disorders. Most haematologists work in both clinical and laboratory arenas.
- Chemical pathology or clinical biochemistry is the study of body chemistry, usually by assaying the levels of substances – electrolytes, enzymes, lipids, trace elements – in the blood or urine. Increasing sophistication of analytical requirements often means that this discipline is at the cutting edge of new technology.
- Immunology is the study of host defences against external threats. Many of these are microbiological, but some are chemical, e.g. foodstuffs. In addition, this is also the study of autoimmunity, when the body's defence systems are turned on themselves (see Chapter 2, pp. 25–26).
- Genetics is the study of inheritance of characteristics and diseases, or a predisposition to diseases. Clinical geneticists, similar to haematologists, are directly involved with patients, whereas laboratory-based geneticists apply the traditional techniques of karyotyping, the microscopic examination of chromosomes in cells in mitosis, and the whole spectrum of modern molecular techniques, such as polymerase chain reaction (PCR), fluorescence *in situ* hybridization (FISH), gene-expression profiling, and DNA sequencing.

Historically, these subjects emerged from the single discipline of 'pathology' which exploded in the mid-nineteenth century, especially in Germany where Rudolf Virchow introduced the term 'cellular pathology'. The divergence of specialities was largely on the basis of the different techniques used in each area. Today, the boundaries between these subspecialities are increasingly becoming blurred as modern techniques, especially those resulting from molecular biology, are applied to all. Cellular pathology remains a critical part of the clinical evaluation of a patient before definitive treatment is offered. Increasingly, some of the roles are also delivered by scientists who are not medically qualified, bringing new opportunities and challenges to building effective multidisciplinary teams.

The editor and almost all of the contributors to this book are primarily histopathologists and it is on this area that the book focuses.

DIAGNOSTIC HISTOPATHOLOGY AND CYTOPATHOLOGY: IMAGES OF DISEASES

Key Points

- Pathology is the study of disease.
- Naked eye examination and the light microscope are the traditional tools of the pathologist.
- Increasingly, molecular biological techniques are applied across the whole spectrum of study of diseases to explore underlying mechanisms.

Cellular pathology, i.e. both histopathology and cytopathology, are essentially imaging disciplines. Its practitioners interpret an image, usually obtained by microscopy, and from it deduce information about diagnosis and possible cause of disease, recommend treatment and predict likely outcome.

Preparing the Image

Tissues or cells are removed from a patient. The fairly simple technique of light microscopy is the bedrock of preparing images. A very thin slice of a tissue, usually about 3 μm thick, is prepared and stained so that the characteristics of the tissue, i.e. the types of cells and their relationships to each other, can be examined. To prevent the tissue digesting itself through the release of proteolytic enzymes, the tissue is immersed in a fixative, usually formaldehyde, which cross-links the proteins and inactivates any enzymatic activity. It is impossible to cut very thin sections of even thickness without supporting the tissue in some medium. Usually the tissue is embedded in paraffin wax, which has the appropriate melting and solidifying characteristics, but freezing the tissue (the principle of the frozen section) and embedding hard tissue in synthetic epoxy resins, such as Araldite, are also done. To stain the tissue section, the vegetable dyes haematoxylin and eosin are traditionally used to distinguish between the nucleus and cytoplasm, and to identify some of the intracellular organelles. It is from examination of sections stained by these simple tinctorial techniques that normal histology and the basic disease processes of inflammation, repair, degeneration, and neoplasia were defined (Figs. 1.1 and 1.2). In the past century numerous chemical stains have been developed to demonstrate, for example, carbohydrates, mucins, lipids, and pigments such as melanin and the iron-containing pigment haemosiderin.

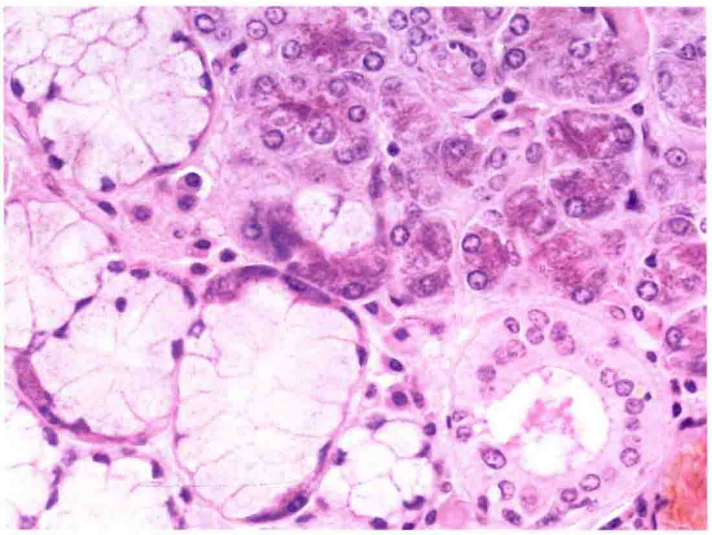

Fig. 1.1 Haematoxylin and eosin (H&E)-stained section of the parotid gland allowing the serous cells (top right), mucinous cells (left), and salivary duct (lower right) to be readily distinguished.

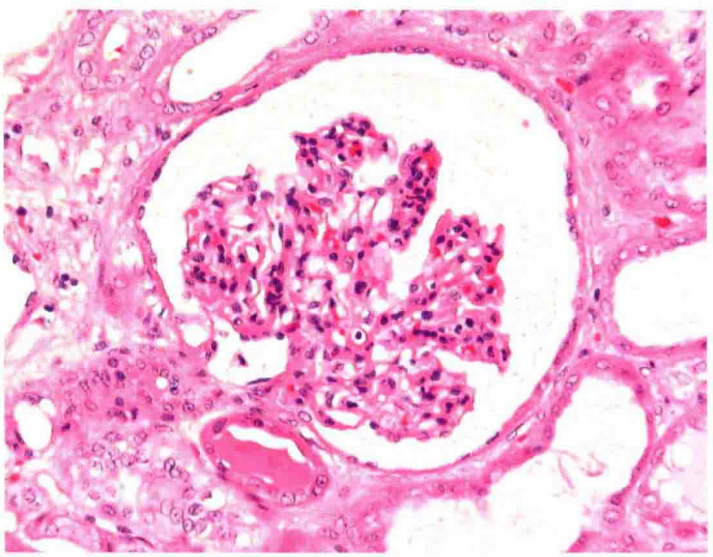

Fig. 1.2 A section of renal glomerulus stained by haematoxylin and eosin. The nuclei have affinity for the basic dye haematoxylin and are blue. The cytoplasm has more affinity for the acidic dye eosin and is pink. This technique has not changed significantly in well over a century.

Refining the Image

Electron Microscopy

Pathological applications of this technique emerged in the 1960s as the technology of 'viewing' tissues by beams of electrons rather than visible light became available. This greatly increased the limits of resolution so that cellular organelles could be identified, and indeed their substructure defined. This allowed more precise diagnosis of tumour types and allowed the structure of proteins such as amyloid to be determined. Ultrastructural pathology now has only a limited place in tumour diagnosis, but still has a central role in the diagnosis of renal disease, especially glomerular diseases (Fig. 1.3) (see Chapter 13).

Immunohistochemistry

This technique evolved in the 1980s and gained a major boost from the development of monoclonal antibodies by the

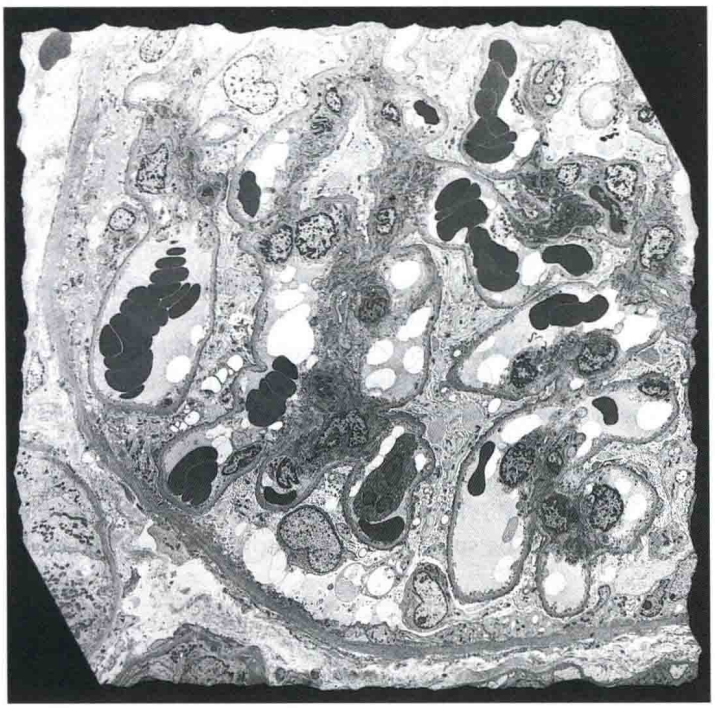

FIG. 1.3 Electron micrograph showing the ultrastructure of a glomerulus. The increased detail is apparent even at this low power.

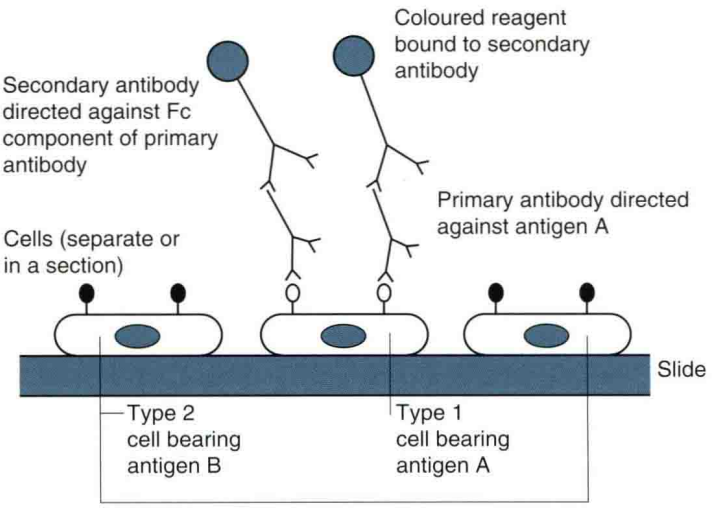

FIG. 1.4 The principles of immunohistochemistry: the aim of the technique is to identify any cell bearing a specific antigen. The cell in the centre has antigens on its surface which are recognized by antibodies, often raised in mice, directed against that antigen. These are the primary antibodies. To demonstrate where these antibodies have bound, a secondary antibody is applied to the section. This antibody is raised in another species, e.g. rabbit. It is directed against the Fc component of the primary antibody and therefore binds to it. An enzyme or fluorescent label is bound to the secondary antibody so that a coloured signal is produced. The cells on the left and right bear different surface antigens, which are not recognized by the primary antibody, and so no signal is produced in relation to them.

late Professor Cesar Milstein. It depends on the property of antibodies to bind specifically to cell-associated antigens. Of course one must beware cross-reactive binding to other unrelated proteins. Tagging such an antibody with a fluorescent, radioactive, or enzymatic label allows specific substances to be identified and localized in tissue sections or cytological preparations. This has proved particularly useful in the diagnosis of tumours, in which it is important to classify the tumour on the basis of the differentiation that it shows to allow the most appropriate treatment to be given. The technique is outlined in Fig. 1.4.

Molecular Pathology

Molecular techniques were the logical next step: rather than attempt to identify proteins within a cell, expression of the genes responsible could be identified if appropriate mRNA could be extracted from the cells or localized to them by *in situ* hybridization techniques. In addition, expression of abnormal genes could be detected, e.g. in several forms of non-Hodgkin lymphoma, specific genetic rearrangements appear to be responsible for the proliferation of the tumour (see Chapter 8, pp. 206–212); their identification allows precise subtyping (Fig. 1.5).

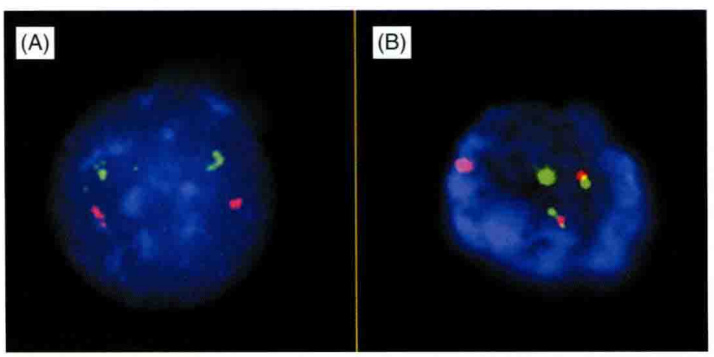

FIG. 1.5 Interphase fluorescence *in situ* hybridization (FISH) on a lymphoma using the *IGH/CCND1* dual fusion probe (Vysis). (A) Normal pattern showing two green signals representing IGH on chromosome 14 and two red signals representing *CCND1* on chromosome 11. (B) Abnormal pattern in a mantle cell lymphoma showing a single green *IGH* signal, a single red *CCND1* signal, and two fused signals representing the two derived chromosomes involved in the t(11;14) translocation. (For more information on the probe used see www.abbottmolecular.com/products/oncology/fish/vysis-ighccnd1-df-fish-probe-kit.html.)

Future Imaging in Pathology

Histopathology sets great store on making the correct diagnosis and gleaning information that is going to be useful in determining treatment options and the probable clinical outcome. In parallel, oncologists are now increasingly aware of how a patient's disease is unique to that patient and treatment must be 'individualized'. The image that a pathologist sees down a microscope reflects the underlying differentiation of the cells and the processes that are taking place. The use of antibodies or RNA detection to identify different cell types and processes adds to this basic knowledge. In recent years the techniques of genomics, transcriptomics, proteomics, and metabolomics have been developed.

In these, the entire DNA profile, gene-expression profile, or protein or metabolic composition of a diseased tissue can be established in comparison to the corresponding normal tissue (Fig. 1.6). Many of these approaches employ high-throughput array-based methods that can generate large amounts of information about normal and diseased tissues: analysis of this information presents a challenge that requires close collaboration with bioinformaticians. The recent development of massively parallel sequencing techniques (next generation sequencing) (see Chapter 3, p. 35) allows the whole (or part) of the genome to be sequenced quantitatively, rapidly, and cheaply, and has the potential to transform the way in which tissue can be interrogated on an individual basis. However, these high-throughput technologies can provide meaningful information only if the tissues being analysed are carefully selected and characterized.

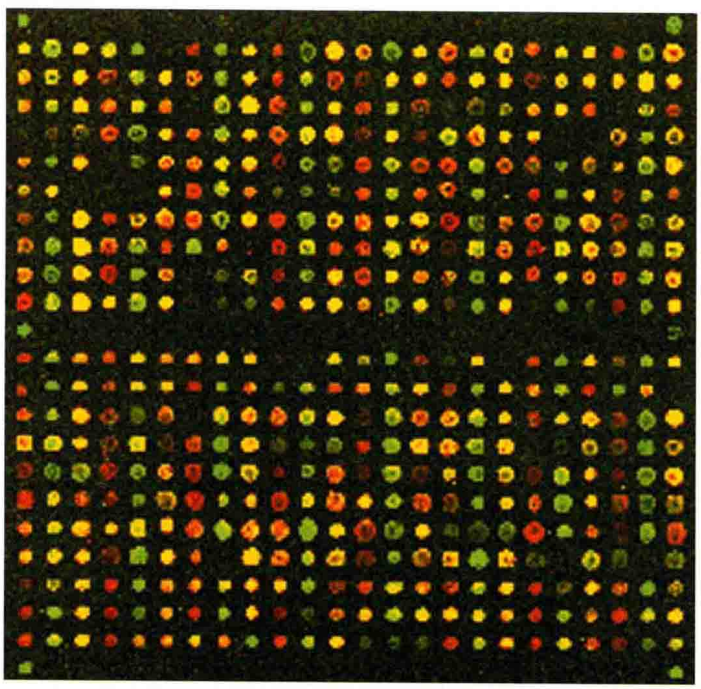

FIG. 1.6 Gene expression microarrays were developed in the mid-1990s and have become a powerful tool to study global gene expression. Real-time polymerase chain reaction (RT-PCR) is used to generate complementary DNA (cDNA) from mRNA extracted from test and control samples. The test and reference cDNAs are labelled with different fluorochromes, in this case represented by the red and green circles. These samples are then competitively hybridized to an array platform that comprises representations of known genes or expressed sequence tags (ESTs), which have been spotted on to a solid support, usually glass or nylon. The presence of specific cDNA sequences in each sample can then be determined by scanning the array at the excitation wavelength for each fluorochrome, with the ratio of the two signals providing an indication of the relative abundance of the mRNA species in the two original samples. Although spotted microarrays are still in use today, the market is now dominated by one-colour platforms such as the Affymetrix GeneChip, in which a single sample is hybridized to each array. Gene expression microarrays have been used in numerous applications including identifying novel pathways of genes associated with certain cancers, classifying tumours, and predicting patient outcome.

Pathology thus has a key role in translational research and should remain at the forefront of medical advances.

HOW RELEVANT IS PATHOLOGY?

Is Histopathology Necessary?

It might be argued that with advances in radiological imaging and other laboratory techniques the role of the histopathologist has decreased. This misses the key point that pathology directly addresses the question of what disease process is occurring and is complemented by many other diagnostic modalities. This role is especially important in the management of patients suspected of having a tumour (see Case History 1.1), but almost all tissues removed from a patient should be submitted for histopathological analysis.

What Can Cytopathology Achieve?

Unlike histopathology, where assessment of the tissue architecture is of prime importance, in cytopathology it is the characteristics of the individual cells that are of most value. Essentially, in diagnostic practice the cytopathologist looks for the cytological features of malignancy (see Fig. 5.3D, p. 80). Admittedly, the relationships between adjacent cells can be appreciated to some extent: e.g. in an aspirate from a breast lump, loss of cohesion between cells is suggestive of malignancy, as is a high nucleus:cytoplasm ratio of the cells (Fig. 1.7). In screening practice, e.g. in cervical cancer programmes, the cytopathologist seeks to identify the same changes but at an earlier stage and thus give a warning of incipient cancerous changes. The biological basis and efficacy of screening programmes continue to be hotly debated.

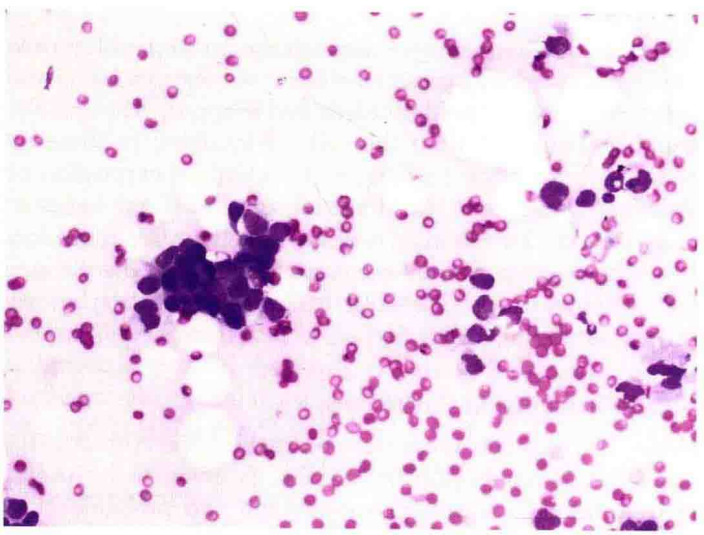

FIG. 1.7 This breast aspirate shows cells with a high nucleus:cytoplasm ratio and loss of cohesion indicating malignancy.

Is the Postmortem Examination a Useful Investigation?

The popular image of a pathologist, perhaps fostered by television programmes, is of an individual who determines the cause of death, especially when foul play is suspected. From the early days of pathology, the postmortem examination has been of importance in understanding disease mechanisms, and in explaining the nature of the individual's final illness. However, advances in imaging and a cultural move not to accept postmortem examinations in many countries have significantly reduced the number performed, other than those carried out for legal reasons. Enormous advances in imaging techniques, especially computed tomography (CT) and magnetic resonance imaging (MRI), when coupled with targeted needle biopsies have to some extent diminished the need for postmortem examinations, but publications continue to show that they uncover hitherto unsuspected conditions.

Establishment of a robust, updated, scientific evidence base for postmortem pathology remains a challenge. Recent events, including the disclosure of widespread practices of retention of tissue and organs for research purposes, have provoked a sea change in public attitudes to postmortem examinations. In some countries specific new legislation is attempting to find the balance of investigation versus prohibition and to provide a platform for education of the public and support of families. Nevertheless, the postmortem examination remains the final arbiter of the cause of death in many cases, the key investigation in the forensic investigation of unexplained deaths, and potentially an essential part of medical audit. This can be so

1.1 CASE HISTORY

The patient, a man of 55, presents with altered bowel habit. Both barium enema and colonoscopy show a stricture at the rectosigmoid junction. A biopsy is taken from this site.

What does the clinician (and of course the patient) want to know?

Is this a benign stricture, perhaps due to diverticular disease or even Crohn's disease? Or is this a tumour and, if so, is it benign or malignant? Fig. 1.8 shows infiltration of the normal tissues by malignant cells arranged in glandular structures, indicating an adenocarcinoma (see Chapter 5, p. 82).

In the light of this diagnosis, the patient proceeds to have a resection of the rectum and sigmoid colon with anastomosis of the cut ends to restore bowel continuity. The specimen is submitted for pathology.

Once again, what information do the clinician and patient require?

- First, confirmation of the diagnosis.
- Second, any information that would predict the likely prognosis of the patient and indicate whether any additional therapy should be given.

This information would include an indication of the type of tumour and an estimate of its biological potential – how malignant it is (its grade), how far it has spread (its stage), e.g. how far through the bowel wall the tumour has spread, and whether the tumour has been completely excised or is present in lymph nodes (Fig. 1.9). To improve the collection of such information in a standard form, the concept of a 'minimum data set' has evolved. The data set recommended by the Royal College of Pathologists is shown in Fig. 1.10.

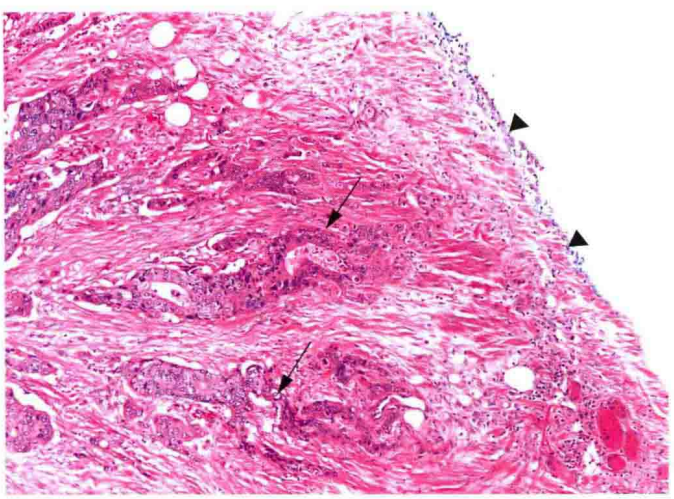

Fig. 1.8 Adenocarcinoma of the colon. Malignant glandular structures (arrows) have invaded the wall of the bowel and have almost reached the peritoneal surface (arrowheads).

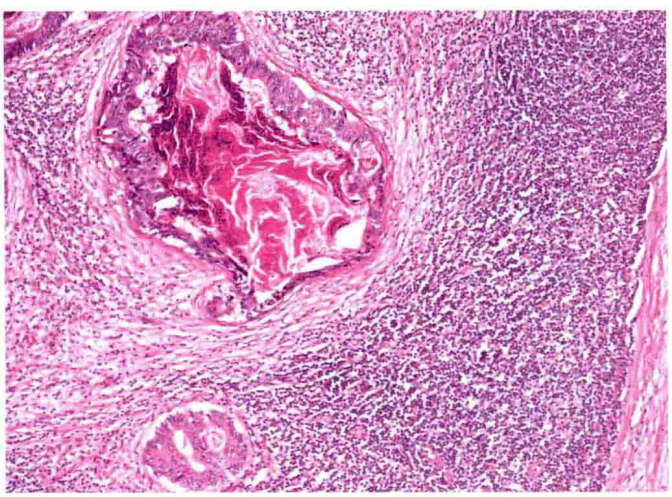

Fig. 1.9 Secondary (metastatic) adenocarcinoma of the colon in a lymph node. Two malignant glands can be seen, with the surviving node to the right. A tumour that has reached the lymph nodes by the time of diagnosis has a worse prognosis.

APPENDIX C PROFORMA FOR COLORECTAL CANCER RESECTIONS

Surname: ..... Forenames: ..... Date of birth: .....

Hospital..... ..... Hospital no: ..... NHS no: .....

Date of receipt: ..... Date of reporting: ..... Report no: .....

Pathologist: ..... Surgeon: ..... Sex: .....

Specimen type: Total colectomy / Right hemicolectomy / Left hemicolectomy / Sigmoid colectomy / Anterior resection / Abdominoperineal excision / Other (state) .....

Gross description

Site of tumour .....

Maximum tumour diameter: .....mm

Distance of tumour to nearer cut end .....mm

Tumour perforation (pT4) Yes ☐ No ☐

If yes, perforation is serosal ☐ retro/infra peritoneal ☐

For rectal tumours:

Relation of tumour to peritoneal reflection (tick one):

Above ☐ Astride ☐ Below ☐

Plane of surgical excision (tick one):

Mesorectal fascia ☐

Intramesorectal ☐

Muscularis propria ☐

For abdominoperineal resection specimens:

Distance of tumour from dentate line .....mm

Histology

Type

Adenocarcinoma Yes ☐ No ☐

If No, other type .....

Differentiation by predominant area

Well / moderate ☐ Poor ☐

Local invasion

No carcinoma identified (pT0) ☐

Submucosa (pT1) ☐

Muscularis propria (pT2) ☐

Beyond muscularis propria (pT3) ☐

Tumour invades adjacent organs (pT4a) ☐

AND/OR

Tumour cells have breached the serosa (pT4b) ☐

Maximum distance of spread beyond muscularis propria .....mm

Response to neoadjuvant therapy

Neoadjuvant therapy given Yes ☐ No ☐ NK ☐

If yes:

No residual tumour cells / mucus lakes only ☐

Minimal residual tumour ☐

No marked regression ☐

Tumour involvement of margins

	N/A	Yes	No
Doughnuts	☐	☐	☐
Margin (cut end)	☐	☐	☐
Non-peritonealised 'circumferential' margin	☐	☐	☐

Histological measurement from tumour to non-peritonealised margin ..... mm

Metastatic spread

No of lymph nodes present .....

No of involved lymph nodes .....

(pN1 1–3 nodes, pN2 4+ nodes involved)

Highest node involved (Dukes C2) Yes ☐ No ☐

Extramural venous invasion Yes ☐ No ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: .....

Background abnormalities: Yes ☐ No ☐

If yes, type: (delete as appropriate)

Adenoma(s) (state number .....)

Familial adenomatous polyposis / Ulcerative colitis / Crohn's disease / Diverticulosis / Synchronous carcinoma(s) (complete a separate form for each cancer)

Other .....

Pathological staging

Complete resection at all surgical margins

Yes (R0) ☐ No (R1 or R2) ☐

TNM (5th edition)

(y) pT ..... (y) pN .....(y) pM .....

Dukes

Dukes A ☐ (Tumour limited to wall, nodes negative)

Dukes B ☐ (Tumour beyond M. propria, nodes negative)

Dukes C1 ☐ (Nodes positive and apical node negative)

Dukes C2 ☐ (Apical node involved)

Signature: ..... **Date** ...../...../..... **SNOMED Codes** T..... / M.....

FIG. 1.10 National Minimum Data Set for Colorectal Cancer. (Reproduced with permission from the Royal College of Pathologists.)

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