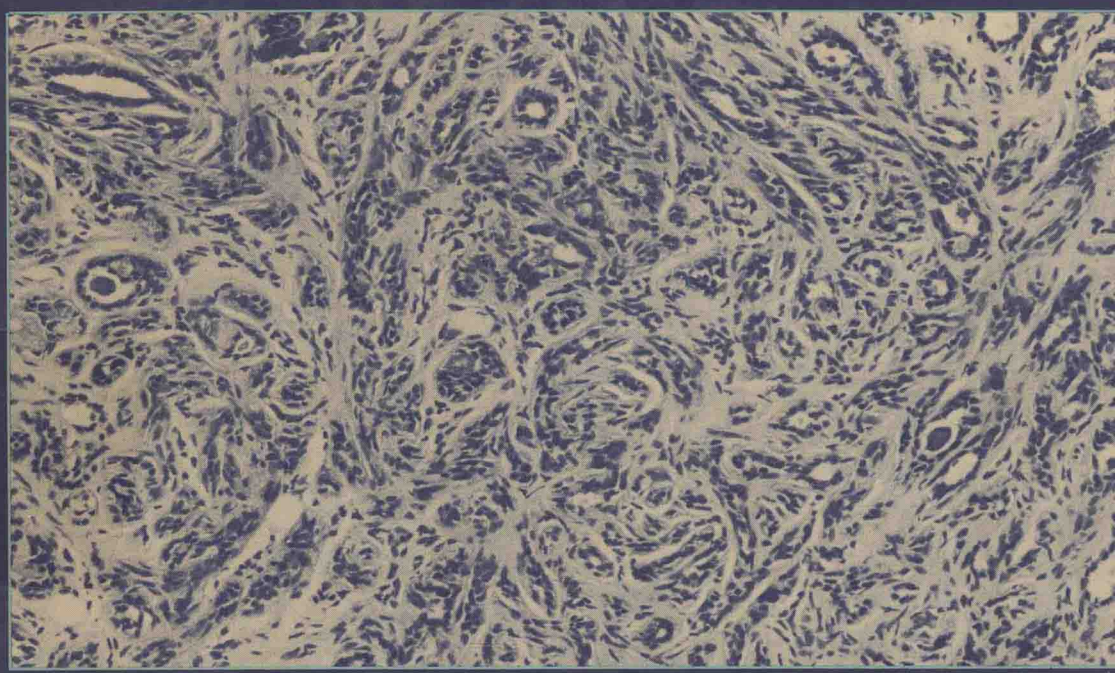
J.C.E.Underwood

Introduction to Biopsy Interpretation and Surgical Pathology



Springer-Verlag Berlin Heidelberg New York

J. C. E. Underwood

Introduction to Biopsy Interpretation and Surgical Pathology

With 71 Figures

Springer-Verlag
Berlin Heidelberg New York 1981

J. C. E. Underwood, MD, MRCPath.

Senior Lecturer in Pathology, University of Sheffield Medical School, and Honorary Consultant Histopathologist, Royal Hallamshire Hospital, Sheffield, S10 2RX, England.

ISBN 3-540-10434-8 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-10434-8 Springer-Verlag New York Heidelberg Berlin

Bibliography: p. Includes index. 1. Pathology, Surgical. 2. Biopsy. I. Title. [DNLM: 1. Biopsy. 2. Diagnosis, Surgical. WO 142 U55i] RD57.U52 616.07'58 80-25572 AACR1
ISBN 0-387-10434-8 (U.S.)

Printed in Great Britain

Filmset and printed by BAS Printers Limited, Over Wallop, Hampshire.

2128/3916-543210

To Ina, Justin, and Claire

Preface

This book is primarily addressed to the needs of the trainee histopathologist. It is intended to bridge that gap between the descriptive histopathology taught as part of the undergraduate medical curriculum and the interpretative skills required of the diagnostician. My object is to convey the basic general principles, in theory and practice. Books are, however, only adjuncts to practical experience and not substitutes for it. Indeed, to obtain the maximum benefit from this book it is essential that the reader is actively involved in the work of a diagnostic laboratory. Only in this way can the trainee become thoroughly conversant with the rudiments of biopsy interpretation.

To retain detailed knowledge of the histological appearances of the plethora of diseases and their permutations to which humans are subject is beyond the mental resources of most individuals. For this reason, histopathologists probably refer to books more often than do most other specialists. This book aims to provide a core of knowledge sufficient to master the fundamental aspects, while still encouraging the intelligent use of all those indispensable atlases, monographs, and fascicles for which there is no substitute.

I make no apologies for beginning the text with a brief account of the history of the biopsy. The origins of biopsy diagnosis might be dismissed as having little relevance to current practice, but it is often easier to understand a subject if one can see how it has evolved and recognise the various ways in which it may continue to develop. Also, it would have been easy to evade the need for a systematic consideration of the actual processes of interpretation. Having decided that the reader should be introduced to heuristics and pattern recognition, I was anxious to avoid giving an idiosyncratic account of something so personal and subjective. I hope I have succeeded in showing that there is nothing particularly arcane about the methods we use to interpret histological images.

The histopathological diagnosis does not begin and end with the inert, two-dimensional, brightly coloured artifact of the stained histological section. It begins with a living patient and ends with a credible report embodying a diagnosis or any other information that may guide the treatment of the patient. Modern investigative techniques may be needed to solve some diagnostic problems and for that reason I have included a general introduction to newer methods of histopathological analysis of proven clinical value. These include electron microscopy, immunological methods, and stereology. Those who work in laboratories without such resources will, I hope, find guidance to the potential usefulness of these relatively sophisticated techniques. Perhaps they will be prompted to seek appropriate help and advice from colleagues who have access to the materials and skills that are necessary to solve some of the more difficult problems that may come their way.

I have referred to published work liberally but not uncritically. I hope that the text will whet the reader's appetite for more information and give directions as to where it may be satiated.

For the trainee, this will be an introduction to biopsy interpretation and surgical pathology in the context of contemporary clinical medicine. The text is an overview and commentary on current theory and practice in histopathology; I would therefore be well pleased if senior pathologists or clinicians also found something of interest and value in these pages.

Sheffield, January 1981 J. C. E. Underwood

Acknowledgements

I am grateful to Professors W. A. J. Crane and L. Henry, in whose Department this book was conceived and produced. My colleagues in the Department of Pathology at the University of Sheffield Medical School and Royal Hallamshire Hospital contributed many useful ideas to the project. Heavily committed to teaching, research, and diagnostic work, they willingly gave me their time and attention to discuss various aspects of the text. I am particularly grateful to Drs. M. E. Boxer, C. D. Franklin, J. R. Goepel, and L. Harvey for their critical appraisal of the entire manuscript and for offering so many useful suggestions. For their advice on technical aspects of electron microscopy and X-ray microanalysis, I thank Mr. T. E. Durrant and Mr. T. Gray. Various general technical points, especially concerning stains, were clarified in discussions with Mr. G. Anderson to whom I am also indebted.

Many colleagues allowed me to use illustrations prepared from their own case material, notably Drs. A. J. Coup, P. Gray, A. S. Hill, M. A. Parsons, C. M. D. Ross, and J. R. Shortland.

Permission to reproduce illustrations from their published work, or unpublished material, was generously given by Dr. J. D. Davies of Bristol, Dr. B. Dixon of Leeds, Professor R. Marian Hicks of London, Professor I. R. H. Kramer of London, and Dr. E. J. Wilkinson of Milwaukee, Wisconsin. I am also grateful for permission from the Editor and publishers of the *Lancet* to reproduce extended quotations from the published works of J. H. Bennett and Ernest Shaw, the Editor of the *American Journal of the Medical Sciences* and Charles B. Slack, Inc. to reproduce an extended quotation from the published work of F. Donaldson, the Editor of the *British Journal of Cancer* and H. K. Lewis and Co. Ltd. to reproduce Fig. 1.1, Dr. J. E. Rhoads, Editor, *Cancer*, and the American Cancer Society to reproduce Figs. 2.4 and 3.14, Professor R. E. Cotton, Editor, *Histopathology*, and Blackwell Scientific Publications Ltd. to reproduce Fig. 7.8, and the Editors and publishers of the *Journal of Clinical Pathology* to reproduce Fig. 8.4. Figure 7.1 was kindly supplied by Philips of Eindhoven.

The quality of the illustrations attests the photographic skills of Mr. M. J. Eaton. The manuscript was typed by Miss Ann Kilner; I am very grateful to her for so patiently working through sheets of illegible draft to produce the finished typescript with such speed and efficiency. Mrs. Rosemary Raine helped with much of the general secretarial work generated by this book.

This project would have remained sequestered in the bottom drawer of my desk but for the enthusiasm and guidance of Mr. Michael Jackson and his colleagues of Springer-Verlag.

My last acknowledgement is my greatest debt. To my wife and children for their understanding and patience.

Explanatory Note

Some clarification of the words "biopsy", "surgical pathology", and "histopathology" is necessary at this point.

"Biopsy" is derived from the Greek –βίος (life) and ὁ ὄψις (view). The word is used in two ways; first, to describe the process of removal of tissue from the living patient for diagnostic purposes (e.g. to biopsy the liver) and, secondly, to describe the actual tissue that has been removed (e.g. a liver biopsy). In both senses the emphasis is on *diagnosis*. "Biopsy" is also loosely used to describe the removal of any piece of tissue from the living body for examination; the examination may just be an assessment of a disease process that has previously been diagnosed (e.g. gastrectomy for endoscopically diagnosed carcinoma).

"Surgical pathology" is a branch of anatomical pathology dealing with the examination of tissues for the diagnosis and guidance in the care of patients; this safely encompasses the strict and loose meanings of "biopsy". At the risk of being pedantic, it must be pointed out that "surgical pathology" is restricted by some dictionaries to the pathology of those diseases accessible to *surgical* procedures.

"Histopathology" is the study of diseased tissues; strictly used, this applies only to cytological and histological structure of the tissues, though some might prefer a broader definition that includes any investigation of diseased tissues. "Diagnostic histopathology" is the application of histopathology to the examination of tissues removed for the diagnosis and care of patients.

I doubt very much whether a panel of linguistic purists would be able to reach a unanimous decision as to precisely how these words should be used.

Contents

1 Diagnostic Histopathology

The twentieth century has seen histopathology develop into a major branch of clinical medicine. While surgeons and physicians continue to bear direct responsibility for the provision of clinical services, investigative and diagnostic specialists are now an integral part of the team that cares for patients. Histopathologists are increasingly involved in work that has a fundamental bearing on the immediate management of patients and are frequently party to therapeutic decisions. The modern histopathologist therefore requires both an intimate knowledge of biopsy appearances and the ability to interpret biopsies in the context of contemporary clinical practice. Before examining the various ways in which the histopathological interpretation of biopsies and surgical resections contributes to clinical practice, the origins of the discipline merit brief recapitulation.

Haruspicy, originating in ancient Babylon, was the art of foretelling the future by studying the organs of slaughtered animals. Some cryptic message latent within the entrails was translated by the haruspex and broadcast to the people (King and Meehan, 1973). The haruspex and the diagnostic histopathologist both prognosticate on information obtained from the examination of tissues. They differ only as do fancy and fact.

A. Origins of Histopathology

The history of histopathology can be divided into two phases. First, the simple recognition and description of the morbid changes in tissues associated with disease. Secondly, the use of such knowledge to identify a disease and to predict its behaviour and susceptibility to treatment in a living subject.

Claudius Galen (130–200) is generally acknowledged to be the first to have given detailed descriptions of the structural changes in the body associated with disease. He constructed a classification of tumours, lesions he attributed to an excess of black bile. In Italy, Marco Aurelio Severino (1580–1656) and Giovanni Battista Morgagni (1682–1771) pioneered the renaissance of morbid anatomy. Severino, in his illustrated book *De Recondite Abscessorum Natura* (1632), classified breast cancer into four different types. However, Morgagni is usually regarded as the founder of modern pathological anatomy. His work, based on a meticulous correlation of the clinical history and autopsy findings, was not merely descriptive but a genuine attempt to understand disease processes. The status of pathology as an independent science was established by Matthew Baillie (1761–1823) with the publication in London of *The Morbid Anatomy of Some of the Most Important Parts*

of the Human Body (1793). An atlas followed a few years later. But it was not until the microscope was applied to the study of diseased tissues that information of potentially diagnostic value was obtained.

Thin sections, necessary for microscopy, could only be cut if the tissue was hardened in some way to prevent deformation. Freezing was simple and effective; wax embedding was still many years away. Sir Everard Home (1763–1832) published pictures of the first histological sections of tumours in his book *A Short Tract on the Formation of Tumours* (1830), but derived few conclusions from them. In Germany, Johannes Müller (1801–1858) in *Über den Feinern Bau und die Formen der Krankhaften Geschwülste* (1838) was able to distinguish different tumours by microscopy.

Among the earliest descriptions of the use of microscopy in the actual diagnosis of tumours and ulcers are those of Bennett (1845) working in Edinburgh, Scotland, and Donaldson (1853) of Baltimore, Maryland. They were the first to show that therapeutically useful information could be obtained from the microscopic examination of tumours and tumour-like lesions. Though they used smears rather than sections, Bennett and Donaldson were largely responsible for transforming human pathology from a purely descriptive discipline into an entirely novel diagnostic method. Their enthusiastic efforts mark the birth of diagnostic histopathology and cytology.

> Another woman, 50 years of age, of cachectic appearance, had for six months an ulcer in the left breast. It was about an inch from the nipple, sunk deep into the substance of the organ, and was about the size of a walnut. Its edges and the surrounding substances were firm and indurated. The glands of the axilla were slightly enlarged. The right breast was healthy. It became a point to determine whether the ulcer was malignant or simple; whether an operation was or was not to be resorted to? An examination of the fluid upon the surface of the ulcer, with the microscope, exhibited—1st. Pus cells, which, on the addition of acetic acid, presented the usual granular nucleus. 2nd. There were several flat scales, presenting all the character of pavement epithelium. 3rd. Were cells of an elongated form, similar to those observed in granulations, and cellular tissues in an early stage.
>
> From these circumstances it was diagnosed that the ulcer was not malignant, and it subsequently disappeared under the use of common applications [Bennett, 1845, referring to the work of Professor Vogel of Munich].
>
> Withing the last year, we ourselves have been able to diagnose cancer in the living subject, in six instances, by nipping off little projecting points of the ulcerated surfaces. In one case, at the request of Professor N. R. Smith, of a patient at the Baltimore Infirmary, when there was extensive disease, with induration and ulceration of a doubtful character, of the penis; in another, by the kindness of my friend, Dr. Van Bibber, in a patient of his, suffering with a tumour accompanied with deep-seated ulceration of the posterior fauces; in a third, a patient of Dr. Maris's, there was a large encephaloid tumour of the neck; in two cases of disease of the neck of the uterus; and in another ulcerated penis. In all, the microscope revealed unmistakable evidences of cancer [Donaldson, 1853].

Credit must likewise go to Lionel Beale, Professor of Medicine at King's College Hospital, London, whose pioneering treatise *The Microscope in Medicine* (1854) firmly established the microscope as a diagnostic tool of considerable versatility. The microscopist could be found "continually fishing for new facts in the excretions of the sick." Much of this early work of Bennett, Donaldson, Beale, and others was done with effusions, exudates, smears, and tissues teased in saline and consequently cytology was regarded as the "senior science" for many years (Bamforth and Osborn, 1958). Only later were sections cut on a regular basis for diagnostic purposes.

The enthusiastic reception that greeted biopsy diagnosis was, in Europe at least, sharply punctuated by the case of the Kaiser's cancer. In 1887, Kaiser Frederick III had a laryngeal lesion biopsied by Sir Morell Mackenzie. The biopsies were reported as benign by Rudolf Virchow in Berlin and, to judge from his published descriptions, the actual tissue submitted to him may well have been free from malignancy (Virchow, 1887). (As so often happens with interesting cases, the blocks

and slides are no longer available for review.) One year later, at the age of 56, the Kaiser died from laryngeal cancer. This infamous case ruined Mackenzie's reputation and started a wave of opposition against the technique of biopsy diagnosis. Virchow, naturally a conservative interpreter of biopsies, was at the forefront of this opposition (Ober, 1970).

Unabated interest in biopsy diagnosis in North America was marked, in the 1890s, by reports from W. H. Welch and T. H. Cullen on rapid frozen section diagnosis during surgical operations. From 1900 onwards, the biopsy was increasingly accepted throughout the medical world as a significant advance. The Kaiser's cancer was quickly forgotten.

The first appearance in hospitals of pathology, as we would recognise it today, evolved from the collecting of museum specimens primarily for educational purposes. This was usually done by physicians and surgeons, many of whom became very skilled at the recognition of gross morbid changes. This practice preceded by some years the identification of gross and microscopic abnormalities in tissues and body fluids as an adjunct to clinical diagnosis.

Rapid advances in pathology ultimately created insuperable difficulties for physicians and surgeons doing histopathology and cytology. The discipline had increased in complexity as more and more knowledge was gleaned from the application of new methods to pathological material. The sheer volume of diagnostic work was also increasing and this necessitated, in most centres, the appointment of a specialist in general pathology who would have responsibility for haematology, bacteriology, and clinical chemistry, as well as for histopathology. Continuing advances in all four subspecialties made unacceptable demands on the general pathologist forced to keep abreast with laboratory work of such diversity. Thus emerged the specialist histopathologists and surgical pathologists.

Diagnostic cytology proceeded along similar lines. Papanicolaou's interest in the cytology of the femal genital tract led, in 1928, to the first report of his studies on cervical cancer at the Women's Hospital of New York City (Papanicolaou, 1928). By the 1950s cervical cytology was used as a screening test for the early detection of this disease. Cytology as an aid to the diagnosis of cancer in other organs developed similarly (Bamforth and Osborn, 1958).

A chronology is given in Table 1.1.

Table 1.1. Historical summary of the development of diagnostic histopathology.

Pre-1800	Descriptive morbid anatomy (Galen, Severino, Morgagni, Baillie, et al.)
1800–1840	First descriptions of tumour histology (Home, Müller, et al.)
1840–1855	Advent of diagnostic cytology and histopathology (Bennett, 1845; Marmy, 1846; Lebert, 1851; Donaldson, 1853)
ca. 1880	Paraffin wax embedding
1887	Biopsy, reported by Virchow, fails to diagnose laryngeal cancer in Kaiser Frederick III
1891	First intra-operative frozen section (Welch)
1928	Diagnostic cytology in cervical cancer (Papanicolaou)
1930–1940	Introduction of needle biopsy techniques
1938	Linderstrøm-Lang cryostat for histochemistry
1941	Fluorescent-labelled antibody technique (Coons et al.)
1943	Application of stereological methods to tissues (Chalkley)
ca. 1950	Electron microscopy applied to tissues
1961	Cryostat used for intra-operative diagnosis (Chang et al.)
1966	Introduction of enzyme (e.g. peroxidase)–antibody conjugates (Nakane and Pierce)
1970–	Application of microspectrophotometry and flow microfluorimetry to tumour biopsies Mathematical treatment (cluster, vector analysis) of diagnostic problems Evaluation of diagnostic fallibility in histopathology

B. The Objectives of Histopathology

I. *Clinical Diagnosis*

The routine conduct of diagnostic histopathology by clinical specialists who have primary responsibilities for patient care is considered by many to be potentially hazardous. The assessment of biopsies objectively and unbiased, in the first instance, by detailed knowledge of the full clinical picture has many advantages. It is easy from the standpoint of a strong clinical conviction to read into a biopsy an interpretation that may be quite unsupported by objective evidence. It is impossible for those who are familiar with a particular patient to be absolutely impartial. Ultimately the pathologist may become familiar with the clinical picture, but the patient will at least have had the benefit of another opinion arrived at independently. There is, however, considerable merit in joint discussions with other specialists at which the biopsy is presented and discussed. The formal participation of histopathologists in clinical teams is now commonly advocated for the management of patients with malignant lymphomas, liver disease, and renal disease among other entities.

Exacting demands are made on the modern histopathologist. Advances in endoscopy and needle biopsy techniques have led to involvement in the diagnosis and management of diseases previously beyond the reach of biopsy; we are now called upon to make more precise diagnoses on smaller and smaller fragments of tissue. Immunology, biochemistry, and physics have contributed an array of new investigative methods, each requiring further interpretative skills to assess the results. Tumours previously dismissed as anaplastic, or perhaps because of arbitrariness or marginal features tentatively placed in a particular category, must now go through the gamut of electron microscopy and immunohistochemistry for marker organelles or substances. Advances in chemotherapy, radiotherapy, and endocrine therapy exactly tailored to specific tumour types must be paralleled by refinements in biopsy diagnosis and classification.

The proliferation of needle and endoscopic biopsy techniques has led to a more detailed understanding of many disease processes and has greatly enhanced histopathological contributions to the care of patients with disorders amenable to both medical and surgical treatment. Biopsies of many organs can now be obtained, though a compromise has to be found between the volume of tissue required for reliable interpretation and that which can be removed from the patient with acceptable safety. Any risks to the patient must be outweighed by the possible therapeutic benefit.

In most hospitals the histopathologist is also responsible for the autopsy service. Although this is traditional, it reflects the continuing interplay between post-mortem findings and the recognition at autopsy of diagnostically useful information that may benefit future patients. The relative clinical independence of histopathologists favours their role as convenors of "Tissue Committees", which investigate allegedly superfluous surgery, and "Death Committees", which police hospital mortality. These audit committees are more popular in North America than elsewhere.

In essence, therefore, the primary clinical role of the diagnostic histopathologist is to provide a reliable and efficient diagnostic service through the interpretation of biopsies and the assessment of surgical resections. Close liaison with clinical teams is vital to the management of many patients.