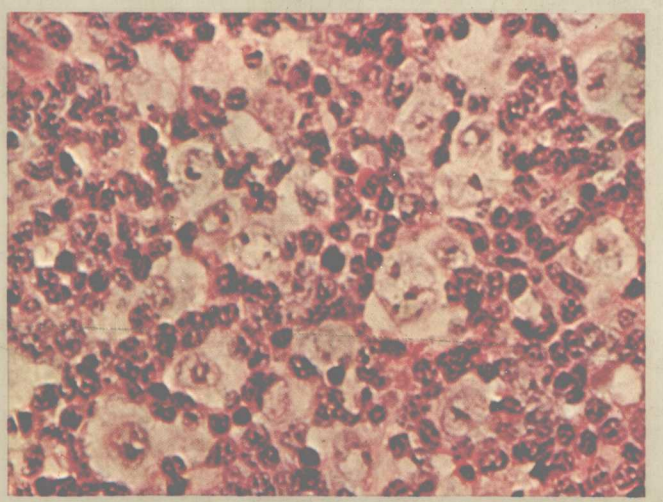
A·H·T· ROBB-SMITH
& C·R· TAYLOR

Lymph Node Biopsy



A DIAGNOSTIC ATLAS

WITH 300 PHOTO-MICROGRAPHS

IN FULL COLOUR

MILLER HEYDEN

Lymph Node Biopsy

BY A·H·T· ROBB-SMITH

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(Chapter V continued)

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PREFACE

IT IS GENERALLY AGREED that the interpretation of a lymph node biopsy is one of the more difficult aspects of histopathology and yet a precise diagnosis is of paramount importance both to clinician and patient. The powerful therapeutic armentarium available for the treatment of Hodgkin's Disease and kindred conditions can have serious effects if administered to a patient with a simple reactive lymphadenopathy, while prompt treatment is essential if complete remission is to be achieved in cases of lymphoreticular malignancies.

This monograph is an attempt to assist pathologists in lymph node diagnosis and is grounded on experience gained from the follow-up studies of the Oxford Lymph Node Registry, the section of Hematopathology and Immunopathology of the School of Medicine of the University of Southern California and other collaborative enquiries in this country and abroad.

In recent years there has been considerable interest in decision theory and the principles of the diagnostic process, with discussion of the relative merits of flow charts, decision trees and clustering techniques in simulated models. It is clear that the histopathologist utilizes, knowingly or not, some form of decision tree or dendrogram in the initial assessment of biopsy diagnosis. Some years ago a pilot scheme using this approach in the diagnosis of lymph node abnormalities was presented in outline and proved popular. It has been greatly expanded in this book with two significant advances:– the provision of coloured photomicrographs of the more important conditions and the introduction of specific methods for cell identification. In conformity with the concept that histological diagnosis is largely a matter of pattern recognition, the photomicrographs are either low power survey views (usually ×40) or high power details (of the order of ×750) of selected fields in which the characters of individual cells can be recognized; it is here that the histochemical and immunohistological techniques are of value in the precise identification of functional cell types which might otherwise be confused.

As this monograph has been written primarily for the hospital pathologist concerned with lymph node diagnosis, rather than for research workers investigating lymphoproliferative disorders, greater emphasis has been placed on classical histology than on electron micrographs or the use of membrane markers in cell identification as these are complex and time-consuming techniques while their interpretation is often far from simple. Nevertheless, a few electron micrographs and illustrations of 'rosetting' have been included where they are really of significance in interpretation.

Presented with a diagnostic biopsy, the first essential is a familiarity with the ordinary appearance of the tissue and the range of variability that can be accepted

as 'normal', and the next is the differentiation of physiological reactive processes from pathological changes. In the case of lymphoreticular tissue, this demands a basic knowledge of 'normal' lymph node architecture and a clear definition of the individual cell types present within the lymph node. Our understanding of lymph node architecture and the response to antigenic stimulation has been much influenced by advances in the theoretical and practical aspects of immunology. In addition there is also an increasing awareness of the radical changes in lymphocyte morphology which may occur as part of the 'normal' response of the lymphocyte to antigenic stimuli. These aspects of lymph node pathology are considered in the first chapter which is primarily concerned with the functional anatomy of the lymph node and the definition of the principal component cells.

Following this there is a discussion of those lymph node structures – cortex and paracortical tissue, follicles, medulla, sinuses etc., – which can be regarded as histological landmarks in the process of diagnosis. These must be looked for and their presence or absence determined: if they are present, whether they are normal or abnormal structurally and in cell content; and if they are absent, how this has occurred. These are the principles adopted here for the recognition of the various pattern of lymph node disease. In addition there may be specific features which enable the pathologist to assign a particular process to a defined disease group or diagnostic entity. Thus certain of the lymphadenopathies possess histological or cytological features which are sufficiently characteristic to allow the distinction of a particular pathological process from other forms of reactive hyperplasia. Similarly some neoplasms possess distinctive histological features which enable the pathologist to make the diagnosis with some certainty.

However, the lymph node has only a limited repertoire of responses to a wide variety of stimuli, and in some cases a reactive condition may simulate a lymphoreticular neoplasm, or vice versa, and so a critical appraisal of all the relevant histological and cytological evidence is of great importance in arriving at a diagnosis.

The application of this approach to a lymph node biopsy forms the major part of this book, in which the different pathological processes encountered are described and illustrated in relation to the diagnostic schema, rather than ordered according to any arbitrary classification. To facilitate orientation, there is, at the beginning of each chapter, an analytical summary with which are linked the running headings together with marginal headings and figure references. As this is primarily a manual of diagnostic histology, it seemed inadvisable to attempt a comprehensive review of the clinical features, natural history and therapeutic response of the various identifiable lymphoreticular disorders, but reference is made to authoritative studies where they exist. On the other hand, it was impossible to evade some discussion of the various nomenclatures and classifications that have come to the fore in recent years. Unhappily, the diverse terminology results in great conceptual difficulties, and forms an impediment to communication amongst clinicians and pathologists. No attempt is made in this book to

propound any new classification or even to champion an existing one, but to avoid confusion the common alternative terms are given wherever this is possible. We have avoided acronyms or abbreviations but have used 'lymphoma' qualified by a suitable morphological epithet for the low grade conditions, restricting the use of 'malignant lymphoma' to those with sarcomatous characters. This approach should assist pathologists and clinicians in integrating published reports, based on one terminology, with their own experience, which may be founded on a distinct system of classification. In this way it is hoped that not only will this monograph assist the diagnostic pathologist, but will also reveal to oncologists, whatever their particular expertise, the problems facing the histopathologist.

THIS BOOK could not have been written without the help and support of many people to whom we should wish to express our thanks.

First to the patients, whose biopsies we studied and then learnt from our clinical colleagues the degree of accuracy and value of our histological interpretations, interpretations that were often influenced by discussion with other pathologists. There are many colleagues who, knowingly or not, have contributed to the observations and concepts set out here, sometimes as joint authors of papers from which quotations appear, and to all of these we are very grateful.

In addition we would wish to express our appreciation of the permission given to us by Professor Saul Rosenberg and Dr. Costan Berard, to include in the Appendix the classification scheme or 'working formulation for clinical usage' which is being put forward by the international panel of the U.S. National Cancer Institute's Non-Hodgkin Lymphoma Study, in the hope that it may reduce the babel of confusion that is hampering lymphoma discussions.

We have been fortunate over the years to have had working with us histological technicians who recognized the importance to our patients of providing preparations of the highest quality, if a reliable diagnosis was to be achieved; it is impossible to clepe all these, but it would be churlish if we failed to acknowledge the help we received from the late Mr. Reginald Duffett, Mrs. Ruby Hughes, Mr. Anthony Chaplin, Miss Maria Hambridge and Mrs. Ysanne Smart. The immunological advances were the result of Mr. J. Burns' initiative and collaboration, while the masterly electron microscopy of Mr. D. Jerome was always available to us.

Our imperturbable secretaries, Mrs. Joan Braidwood and Mrs. Vera MacIntosh typed and re-typed our original manuscripts, each in its own way almost indecipherable, and subsequently a host of secretary cryptographers have unravelled scarcely legible amendments and alterations. We are grateful to Dr. Anita Borges for reading the book in manuscript and also deeply indebted to Dr. Parry, Messrs. Cousin and Reed, who prepared with infinite care the photomicrographs which were translated into admirable coloured illustrations by the skill of Cliché Schwitter of Basle.

However, this book would never have been completed but for the enthusiasm,

knowledge and tolerance of Mr. Harvey Miller, whose sensibility was able to translate all our ill-defined ideas into the reality of print, while accepting with tranquility our over-enthusiastic estimates of the time involved in consummation.

In the later stages, when galley proofs and photographs were changing into pages of type and plates, it was the artistic precision of Mrs. Elly Miller, who could turn with equanimity from miniatures in illuminated manuscripts to colour requirements of immunoperoxidase preparations, that ensured that the book was both typographically and orthographically correct; indeed, we often felt that her name should appear on the title page as editor, if not co-author.

The research work which generated this book was originally supported by the British Empire Cancer Campaign and the Lady Tata Memorial Fund, and more recently by the Leukaemia Research Fund, the research funds of the United Oxford Hospitals, the Medical Research Council of the United Kingdom as well as groups from the National Institute of Health in the United States of America. We can only hope that it may play some part in the achievement of the objectives for which these charitable and governmental funds were established.

We dedicate this book to our families
who have given us support and encouragement
during the years that this incubus was nurtured

CHAPTER I

THE HUMAN LYMPH NODE

Component cells and functional anatomy; Principles of lymph node diagnosis

ANALYTICAL SUMMARY

1. **Technique of Lymph Node Biopsy**
   Aspiration and Drill Biopsy – handling of lymph node biopsies in the laboratory – preparation of bone marrow – preparation of spleen – staining techniques
2. **General Structure of the Lymph Node**
   Component cells – general anatomy of the node
3. **Patterns of Lymph Node response**
   Humoral immune response – cellular immune responses – histiocytic responses
4. **General Principles in the Examination of a Lymph Node Biopsy**

THE ASSESSMENT AND DIAGNOSIS of lymph node disorders must be based upon a sound knowledge of the basic nodal architecture and a recognition of the morphological changes occurring during the normal functioning of the lymph node. Traditionally, the 'range' of reactive responses has been determined by experience and one of us has maintained an active interest in lymph node pathology for more than forty years. However, advances in experimental immunology during the past decade have profoundly influenced our concepts of lymph node function and anatomy. Generally, histopathology has been slow to assimilate this new information and, until recently, little account has been taken of the radical changes in morphology occurring during 'transformation' of the small lymphocyte in response to contact with specific antigen.

In this chapter the component cells and architectural features of the resting lymph node will be related to current immunological concepts, and the basic patterns of the immune responses will be examined.

1. Technique of Lymph Node Biopsy

Recognition of the more subtle elements which are of value in the diagnosis of lymph node disorders, is vitally dependent on adequate biopsy and on proper fixation and processing.

The *Selection of the Biopsy Site* is to a large extent determined by the location of the enlarged nodes, or by an abnormal lymphangiogram. However, in the absence of definite clinical indication, the nodes of election for histological diagnosis are from the low cervical region or axilla. Inguinal nodes are commonly

scarred, while upper cervical nodes frequently show some degree of reactive hyperplasia which may obscure a more significant change. These difficulties were clearly illustrated in a study reported by Saltzstein (1965). In biopsies of sixty-eight patients a diagnosis was reached in 64% of supra-clavicular nodes, and in nodes from other sites as follows: cervical 46%, scalene 36%, axillary 27% and inguinal 22%. Of thirty-five patients in whom the biopsy was not diagnostic, six were subsequently shown to have a serious lymph node disorder, emphasizing the importance of selecting the biopsy site, even if lymphadenopathy is widespread.

The ultimate decision is of course the prerogative of the surgeon, but certain principles apply. One or more nodes should be removed intact with a minimum of trauma. If possible the surgeon should be dissuaded from a close dissection of the nodes, as this can result in the capsule remaining within the wound while the pathologist only receives fragments of lymphoid tissue. It is much to be preferred if a reasonable amount of the periadenoid tissue is included in the biopsy. This procedure requires an adequate incision with good exposure, and small biopsies taken under local anaesthesia are seldom satisfactory.

When a group of nodes is involved, it is advisable to remove both superficial and deep nodes, for the former may show only reactive features, while the deeper and less accessible nodes are involved by some process of serious clinical import; Slaughter et al (1958) displayed this in their studies of cervical block dissection in Hodgkin's disease.

Aspiration and Drill Biopsy have their advocates, but have proved unrewarding in our hands. It is true that, by these methods, samples of tissue can be obtained under local anaesthesia with little inconvenience to the patient, and there is no doubt that lymph node aspirates, if handled properly, can provide excellent cytological detail. However, this can equally well be achieved by making imprints from excised nodes as will be described later. The major disadvantages of these techniques are the risk of cellular trauma and distortion, and the possibility that the fragments obtained could be too small to reveal the relationship of the various cellular and structural elements, on which accurate diagnosis largely depends. It may be possible to state that the sample includes malignant cells, and that these are from a carcinomatous metastasis or malignant lymphoma, and on occasion it is possible to diagnose a particular granulomatous process. However, in our experience this type of biopsy is quite unsuitable for recognition of the subtle features of many lymph node disorders, and all too frequently microscopical examination fails to achieve a definite diagnosis. Thus, the patient, having suffered the discomfort of aspiration, must then be subjected to a full surgical procedure.

The Handling of Lymph Node Biopsies in the Laboratory

Ideally the intact unfixed lymph node should be presented immediately to the pathologist, who then has the opportunity of selecting suitable portions for