Malignant Lymphomas

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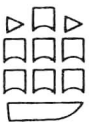

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Foreword

How many pathologists enjoy wrestling with the diagnosis of lymphoid neoplasma? And having made the diagnosis of lymphoma who appreciates the intellectual pyrotechnics involved in reconciling the various classifications, now rabbinical in their complexity?

It is highly probable that many of these problems, diagnostic and logical, emanate from the failure of pathologists generally to get to grips with the biology of lymphoid neoplasia. Thus this volume by Ian Lauder and John Habeshaw is extremely timely. In it the major problems in lymphoma pathology are stated, classification and epidemiology critically discussed, and the cell and molecular biology, now of increasing importance in diagnosis, succinctly described. Naturally enough, histogenesis and cell lineage in lymphomas, eternally fascinating to pathologists, figure largely, but the impact of these newer ideas on treatment and prognosis is not forgotten.

We are certain that this volume will occupy a unique and prominent place in the now burgeoning literature on the subject — a very necessary reading for lymphoma tyros and aficionados alike.

London
1988

N.A. Wright
J.G. Azzopardi

Preface

> Day by day do those who are obliged to consume their best energies in the frequently so toilsome and so exhausting routine of practice, find it becoming less and less possible for them, not only to closely examine, but even to understand the more recent medical works. For even the language of medicine is gradually assuming another appearance . . . .
>
> Rudolf Virchow; Preface to the First Edition of *Cellular Pathology*,1858

Some things have changed remarkably little in the last century, but the pathology of malignant lymphoma is not one of them. Even in the relatively short interval between the conception of this volume, and its appearance in draft, new and relevant material forced several of our contributors to revise extensively their contributions. Even so, it is certain that some of the detailed observations will be superseded and some of the more speculative conclusions modified by new data before this volume appears in print. The editors see this volume less as a compendium of fact, than as a vehicle for factually based ideas. The various authors have tried to show how, in their particular case, our views may need to be modified to cope with the explosion of current technology and new information threatening to engulf those active in this discipline. Wherever one chooses to look, from epidemiology to histological diagnosis, from molecular biology to staging and treatment, ideas are on the move.

Progress in understanding does not unfortunately equate with ability to generate data, and we need to avoid replacing one kind of dogma with another. Being able to pronounce on the B or T cell content of a malignant lymphoma (even in paraffin section) is interesting from an historic viewpoint, but such information is only relevant if it can for example be placed in the context of the disease's epidemiology or molecular biology as predictor of biological behaviour. The complexity of this single class of disease is such that it exceeds our capacity even to ask the right questions, far less receive consistent and satisfying answers. The reality of malignant lymphoma lies beyond the reach of this book, and probably beyond current knowledge. It is perhaps enough to know, however unusual the malignancies of lymphoid cells will eventually prove to be, that their study is an important step in understanding the general nature of cancer despite its many different forms. To those who might be distressed by the concept that Hodgkin's Disease may be only another form of 'non-Hodgkin' lymphoma, or by the view that epidemiological studies without

a proper pathological base are of little value, or by any other opinion herein, Virchow's opinion is still apt:

> In a science so directly practical as that of medicine, and at a time when such a rapid accumulation of facts is taking place, as there is in ours, we are doubly bound to render our knowledge accessible to the whole of our professional bretheren. We would have reform, and not revolution: we would preserve the old, and add the new. But our contemporaries have a confused idea of the results of our activity. For only too much is apt to appear as though naught but a confused and motely mass of old and new might be obtained; and the necessity of combatting rather the false or exclusive doctrines of the more modern, than those of the older writers, produces the impression that our endeavours savour more of revolution than reformation. It is, no doubt, much more agreeable to confine oneself to the investigation and simple publication of what one discovers, and leave it to others to exploit it, but experience teaches us that this is extremely dangerous, and in the end only turns out to the advantage of those who have the least tenderness of conscience.

We have learned much by editing this book, and hope that the readers are similarly rewarded.

London and Leicester — J. A. H.
1988 — I. L.

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(J.A.H).

I gratefully acknowledge the help of Mrs. Geraldine Holmes without whose tireless help the preparation of this book would have been impossible. I am also grateful to Dr. Kevin West and Dr. Howard Pringle for their help with the illustrative material.

(I.L.)

We both acknowledge the continuing help and advice received from various members of the British Lymphoma Pathology Group during the writing of this book.

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1988

J. A. H.
I. L.

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INTRODUCTION

Pathological science is that branch of biology which deals with those changes of form and constitution of the living body occasioned by a diseased state. Our understanding of normal physiology is incomplete. This is particularly true of the immune system, consequently the pathophysiology of those diseases affecting the immune system is often ill understood.

One possible solution to this problem is to study disease states, which by their existence in groups of common form, shed light on normal physiological processes. For example the discovery that lymphoma or myeloma is, in a general sense, a clonal disease has given considerable strength to the idea that many forms of neoplasia may be clonal in origin. However approximate this notion may be, there is no dispute about the overall impact this discovery has had upon subsequent scientific behaviour in investigating the oncogenic potential of abnormalities in those cells specifically associated with malignant disease.

Pathology or, to be more specific, pathophysiology, is a scientific discipline extending beyond enquiries into normal form and function into the area correlating abnormal form and dysfunction with specific disease. In contrast with the great pathologists of the last century, the current generation of pathologists often appear to prefer erudition in specific diagnosis to the more expensive and less utilitarian practice of pathophysiology. This regrettable tendency does constitute a problem in developing strategies to cope with future developments in pathology. As apparent from other published and projected volumes in this series the advances made possible by development of current technology alone will alter the diagnosis and treatment of the common diseases within the professional lifetime of most readers of this book. Pathological science will have to adapt, to cope with both the technical advances at the bench and with the conceptual advances resulting from them.

In a broad sense, the purpose of this book is to project the climate of ideas currently associated with the pathophysiology of malignant lymphoma, and to predict areas in which the development of these ideas is of some potential importance in diagnosis, understanding and treatment of lymphoid malignan-

cy. The topics covered inevitably reflect the current interests of the various contributors and limitation of space have resulted in some gaps in the overall content. Despite this, we believe those involved in the disciplines of histopathology, immunology, haematology and oncology will find much of interest in this volume.

Our volume begins with an account of the epidemiology of malignant lymphoma where the many risk factors significantly associated with the disease state act through a common cause. This cause can be identified as the conjunction of the immune system in an individual made susceptible by his or her genetic constitution with a promotional, or lymphomagenic, event. Since many identifiable risk factors affect immunological integrity, but lymphoma is not universal, indicates that risk is defined on an individual basis, even to potent lymphomagenic agents. The problem identified here in the epidemiology of lymphoma is how to link the genetics of the individual with the response of that individual to the apparent lymphomagenic agent.

There follows from a series of contributors, a discussion of the nomenclature, classification and immunology of malignant lymphoma. From extensive studies of lymphoma phenotype there is now almost universal appreciation that malignant lymphomas of different types are lesions representative of equivalent normal lymphoid tissue compartments, and are composed of the lymphoid cellular elements these compartments normally contain. Follicular lymphoma is now considered by many as a 'neoplasm of follicular B cells' although it might more appropriately be termed a 'neoplasm of germinal centres'.

Phenotypic heterogeneity in lymphoma affects cells of the neoplastic clone. For example, in thymic lymphoblastic lymphoma, clonal populations can exhibit forms varying from very early T cells (TdT+, OKT6+) to more mature cell types (OKT6+, OKT4/T8+) within a single neoplasm. In general, however, the impression from phenotyping is of an identifiable lineage of neoplastic cells, of clonal origin, retaining a fidelity of phenotype appropriate to the tissue compartment from which they originate. In other words, the 'maturation arrest' associated with neoplasms of this kind is in truth an abnormally expanded compartment of cells in one phase of normal differentiation. There are examples to be found in the ontogeny of the lymphoid system where the differentiation compartments of lymphoid cells vary enormously in size with age. In the neonate, much of the lymphoid tissue is thymic. Shortly after birth, there is rapid expansion of the B-cell system, and marked development of B-lymphoid tissue in the gut. It has long been noted that the different presentations of childhood lymphoma, as well as the age-related incidence of B- and T-cell neoplasms, follows a pattern predicted by ontogeny.

B and T cells in different differentiation compartments have different functions. Residence in a particular differentiation compartment implies 'function' as well as 'differentiation', and might suggest that 'maturation arrest' is not necessarily a cellular defect, but may also be a functional deficiency of that lymphoid tissue compartment. So the presence of T-lymphoblastic lymphoma in the neonatal thymus might signify defective thymic function

rather than a constitutional defect of T lymphoblasts. What has remained obscure until recently, was the likely function of the thymic differentiation compartment. It is now known to be the site of proliferation and selection of a relatively few clones of T cells, on the basis of their T-cell receptor gene rearrangements.

We are thus constrained to believe that malignant lymphoma affects all the formed elements of the immune system, and cannot justifiably be split into entities defined *only* by the preponderance of one cell type. Follicular lymphoma, for example, appears as a distortion of the normal architecture and functional interplay of diverse cell populations identifiable phenotypically as equivalent to those normal B and T cells which produce secondary immune responses to antigenic challenge. This is also true of lymphomas which are derived from mucosa-associated lymphoid tissue and probably also true of Hodgkin's disease. Whether it is true of neoplasms derived from antigen-presenting cells, such as the histiocyte, we leave the reader of this volume to decide!

Adequate studies of malignant lymphoma demand close examination of the cellular constitution of the lesions, abnormalities of cells within the lesions, and the several contexts in which such abnormalities are found to coexist with the malignant state. Of fundamental importance in our understanding of how the malignant state develops is a knowledge of those cytogenetic changes which accompany the development of a neoplasm. The effects of the cytogenetic alterations are to uncouple the processes of cell growth and differentiation. Specific cytogenetic abnormalities, particularly those involving oncogenes, relate to normal mechanisms of growth of differentiated cells. In the neoplasm discrete cytogenetic abnormalities may confer selective growth advantages, but are expressed according to the stage of differentiation of malignant cells. Chromosomal abnormalities correlate with the type and class of lymphoid cell represented in the neoplasm as having typical phenotypes of precursor, or differentiated normal cells. For example, chromosomal abnormalities involving the HC rearranging sites on chromosome 14 typify lesions which, phenotypically, are composed of B cells which normally undergo HC rearrangements at an equivalent stage of differentiation. As discussed in Chapter 5, attempts to prove a correlation between selective growth advantage and the precise location of the translocation using Burkitt-derived lymphoma cell lines and EBV-transformed lymphoblastoid cell lines merely emphasise this close relationship between the specific translocation and differentiated state. Burkitt lymphoblasts are not derived from B cells of an equivalent stage of differentiation to ebu-transformed B cells of peripheral blood; and tumorigenic potential in the latter is not dependent upon chromosome 14 changes. The key problem, then, is not solely concerned with 'translocation conferring selective growth advantage', but with the more appropriately obscure topic of why such translocations are expressed in relation to the state of differentiation of malignant cells.

It is difficult to avoid here a conceptual clash between theories which invest all oncogenic potential in an altered cell, and those which allocate the oncogenic

process to a defective interaction between cells and the host. In the former case, cells select themselves by virtue of the causal association between the genomic event and an intrinsic growth advantage conferred by a quantitatively or qualitatively altered oncogene product. In the latter case cells are selected by their normal capacity for growth in a system where stimuli inducing growth act in a specific and unregulated fashion. There is no dispute about the fact of occurrence of specific cellular abnormalities, nor about the operation of selective processes acting upon neoplastic malignant cell populations. There is a difference in determining where (i.e. at which point in differentiation) selective processes act, and in allocating the acquisition of specific genomic abnormalities to a point prior to selection or to any point following selection of the malignant population.

In malignant lymphoma this kind of dispute is of more than academic importance, as it has profound implications on how we approach the problem of effective therapy in the future. If the specific defect lies within the host, and not within an intrinsically altered malignant population, rational therapy would depend upon correcting the former, rather than eliminating the latter. Because of its importance, we have identified this area as one of the key problems awaiting resolution.

Technical and conceptual advances in a subject are all very well, but what of the patient? The role of the pathophysiologist is a tightly defined one—that of understanding the mechanisms of disease, and by that knowledge contributing materially to the welfare and treatment of patients. In the field of malignant lymphoma, the steady trickle of new information has produced positive benefits. The appreciation, through better morphology and phenotyping, that the majority of childhood lymphomas were closely related to the common childhood leukaemias, has been partly responsible for the inprovements in therapy now routinely used in this class of disease. Knowledge of the subtypes of adult B-cell disease has enabled a more rational approach to therapy in these conditions. The recent description of the HTLV-I-associated neoplasms is yet another instance where correct identification of a malignant cell subtype (the T cell) enabled rapid progress to be made in seeking the associated virus, and working out the aetiology and pathogenesis of a rare but important variant of T-cell disease. However, it is true to say that progress for the clinician in treating lymphoma has been largely confined to the refining and rationalisation of empirical treatment schemes in the light of experience. Better diagnosis does not always benefit the patient if the available therapy is not adequate in the first instance. This is not a clinical failure, but is a reflection upon the inadequacy of the science, which has consistently failed to develop new forms of therapy appropriate for the disease. Low-grade, indolent B-cell lymphoma of follicular class does not respond well, in the long term, to any conventional therapy. Reserving treatment does not appear to harm the prospects of later palliation, and not treating selected groups of patients, may, paradoxically, indicate a real, though minor, therapeutic advance. Bone marrow transplantation, and the use of immune modulating reagents therapeutically are currently on trial. The

greatest therapeutic success is undoubtedly the rational use of radiotherapy and combination chemotherapy directed by staging in Hodgkin's disease, although concern is being expressed about the late incidence of second tumours, particularly lymphoma and leukaemia, in effectively treated patients.

Where laboratory science has modified the clinical approach is in the new diagnostic technology available through better imaging techniques, and the use of labelled monoclonal antibody probes. The natural growth in the fields of drug targeting, and detection of small secondary deposits or residual tumour, are distinctly encouraging signs of further therapeutic advances to come.

The contributions to this book illustrate how the combination of good work and enthusiasm bring within reach of solution many of the problems believed to be insoluble not so long ago. The debate about the nature of these diseases should, before long, be satisfied by understanding the biology of specific defects in malignant cells, and in the immune system which contains them. Consequently there will follow a deeper understanding of the problems of prevention and cure. This will only be achieved by hard work, and the proper support of the laboratory and the clinician by those empowered, and thus entrusted with the responsibility of so doing.

Epidemiology of malignant lymphoma

The epidemiology of malignant lymphoma presents particular difficulties. These stem from the heterogeneity of this disease group and also reflect the changing state of knowledge of different subtypes clinically, histologically and immunologically. In recent years major advances in monoclonal antibody studies and cytochemical techniques have enabled more precise definition of cell populations and led to new classifications, particularly of non-Hodgkin's lymphomas (NHL). These advances in laboratory techniques have been slow in being incorporated in epidemiological analyses.

Descriptive epidemiological investigations have usually employed the criteria of the International Classification of Diseases (ICD). This is revised each decade; the latest (9th revision) was published in 1977 (WHO 1977). ICD classifications of NHL and Hodgkin's disease (HD) have changed little since 1948. The main changes in recent editions have been the separate classification of entities such as mycosis fungoides (MF), Sezary's syndrome and hairy-cell leukaemia (HCL), and the adoption of the Rye modification of the Lukes-Butler classification of HD. Table 2.1 shows the most recent ICD 9th revision. Such limited classifications are of little use to modern analytical epidemiological investigations.

DESCRIPTIVE EPIDEMIOLOGY

Descriptive published statistics for lymphoma should be interpreted with caution, because of variations in diagnosis and classifications, and also because they may be influenced by wide variations in registration procedures and in the quality of case certification/verification. Since 1966 incidence data from selected cancer registries world-wide have been summarised in Cancer Incidence in Five Continents (CI5), the most recent volume appearing in 1982 (Waterhouse et al 1982). CI5 refers only to the major ICD categories 'NHL', 'HD' and 'other neoplasms of lymphoid tissue'. Incidence details from selected countries appear in Table 2.2. Observed differences may occur for several reasons—some could be artificial due to constraints of registration, others

Table 2.1 ICD 9th revision (1975).

200 *Lymphosarcoma and reticulosarcoma*
200.0 Reticulosarcoma
200.1 Lymphosarcoma
Excludes: lymphosarcoma-cell leukaemia (207.8)
200.2 Burkitt's tumour
200.8 Other named variants
Reticulolymphosarcoma

201 *Hodgkin's disease*
Note: Two alternative subclassifications are given: .0–.2 Parker-Jackson
.4–.7 Rye modification of Lukes-Butler
201.0 Hodgkin's paragranuloma
201.1 Hodgkin's granuloma
201.2 Hodgkin's sarcoma
201.4 Lymphocytic-histiocytic predominance
201.5 Nodular sclerosis
201.6 Mixed cellularity
201.7 Lymphocyte depletion
201.9 Unspecified

202 *Other malignant neoplasms of lymphoid and histiocytic tissue*
202.0 Nodular lymphoma
Brill-Symmers disease
Follicular lymphoma
202.1 Mycosis fungoides
202.2 Sezary's disease
202.3 Malignant histiocytosis
202.4 Leukaemic reticuloendotheliosis
Hairy-cell leukaemia
202.5 Letterer-Siwe disease
Acute differentiated progressive histiocytosis
Acute infantile reticuloendotheliosis
Excludes: histiocytosis (acute) (chronic) (277.8)
histiocytosis X (chronic) (277.8)
202.6 Malignant mast-cell tumours
Malignant: mastocytoma Mast cell sarcoma
mastocytosis
Excludes: mast-cell leukaemia (207.8)
202.8 Other lymphomas
Lymphoma (malignant)
NOS
Diffuse
202.9 Other and unspecified

could be real and include differences in genetic susceptibility, socio-economic development or exposure to environmental hazards. These differences can be examined further in more detailed studies. Tables 2.3 and 2.4 give incidence information from England and Wales for lymphoma in adults and from Great Britain for children (OPCS 1979, 1981, 1985; Draper et al 1982).

Age

The age distribution of NHL varies geographically. In economically developed