Hodgkin's Disease

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Preface

In the last 20 years our knowledge of the biology of Hodgkin's disease has greatly increased, and this has been paralleled by changing ideas about its management. For example, the lessons learned from staging laparotomy have allowed the more accurate selection of patients for radiotherapy. Knowledge of the prognostic factors associated with survival have allowed us to make management decisions without resorting to surgical staging. The introduction of combination chemotherapy gave a curative treatment for the first time in patients with advanced disease, and this development has pointed the way for new approaches to the drug treatment of other cancers. Knowledge of the histopathology and cellular biology of Hodgkin's disease is already influencing treatment choices, and we await the impacts of cell phenotyping and molecular biology upon the clinic.

We think that these considerations make a new book on Hodgkin's disease timely. No comprehensive text has appeared since the second edition of Kaplan's classic monograph in 1980. That excellent work stood as a monument to his lifetime interest in the disease and encapsulated the practice at Stanford that was so influential worldwide, while in Britain Sir David Smithers' book gave a comprehensive account of the practice current in the seventies. However, already things have changed. In planning this book we have tried to produce a comprehensive text covering the important biological and clinical aspects of Hodgkin's disease. It is an attempt to represent a wide range of views from Europe and North America and we hope that the book will serve as a survey of our present knowledge of Hodgkin's disease and an outline of the basis upon which future research can be done. There has been no attempt to avoid controversy, particularly where principles of management are concerned, but the opinions of the contributors are also those of the editors and we hope that this has led to a fair measure of consistency.

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Introduction

P. SELBY & T.J. McELWAIN

Hodgkin's disease has always attracted attention out of proportion to its incidence. Its striking clinical characteristics, occurrence in relatively young patients, and complex histopathological features partly explain this. Lately the principal clinical developments have been new curative treatments and changes in the investigation and staging of the disease as these treatments have been altered.

The history of the development of our understanding of Hodgkin's disease has been well reviewed by Kaplan in his classic monograph (Kaplan 1980). Thomas Hodgkin at Guy's Hospital in London described the morbid anatomy of the condition in a paper read in January, 1832. The condition was named Hodgkin's disease by Samuel Wilks in 1865 who further characterized it as involving gross lymphadenopathy and 'a deposit of a morbid kind in the internal viscera, more especially in the spleen.' The history of our understanding of the disease from this date may briefly be summarized:

Sternberg (1898) and Dorothy Reed (1902) identified the characteristic giant cells of Hodgkin's disease. A less clear description of these cells, which are commonly referred to as Reed-Sternberg cells, was made by Olivier and Ranvier (1867), Tuckwell (1870), Langhans (1872), Greenfield (1878) and Gowers (1878). Further histopathological characterization was made by Jackson and Parker in 1947, and the modern histological classification of Lukes and Butler was adopted at The Rye Symposium on 'Obstacles to the control of Hodgkin's disease' in 1966.

The modern staging classification followed the Ann Arbor Conference (Carbone *et al.* 1971) and use was made of lymphography introduced by Kinmonth *et al.* in 1955 and of staging laparatomy with splenectomy to evaluate the intra-abdominal extent of Hodgkin's disease, hitherto often undetectable by clinical means (Glatstein *et al.* 1969).

Pusey (1902) was the first person to treat Hodgkin's disease with radiotherapy, and by the 1930s Gilbert (1939) could report radiation-associated cures in patients with localized disease at presentation. The concept of extended-field radiotherapy was refined in the 1940s and 1950s by Peters in Toronto (1950). Supervoltage radiotherapy was first used for extended-field radiation in the 1950s by Henry Kaplan at Stanford University in California (1962, 1966).

Single-agent chemotherapy started with alkylating agents and was a by-product of wartime work on the development of mustard gas (Goodman *et al.* 1946). Effective combination chemotherapy was developed in the 1960s at the National Cancer Institute in Washington (De Vita *et al.* 1970), having been shown already to raise the remission rate in acute lymphoblastic leukaemia. This was soon followed by the recognition that

some patients could be cured by chemotherapy (De Vita *et al.* 1980). The success of combination chemotherapy in Hodgkin's disease stimulated the development of modern medical oncology and the idea of combination chemotherapy for solid tumours was built largely upon experience gained from Hodgkin's disease.

The simultaneous introduction of so many changes during the 1960s and 1970s has completely altered our approach to Hodgkin's disease and made it difficult to assess the contribution of each new technique or treatment. During the last two decades work has, in many centres, sought to evaluate these new developments and put together a logical and successful approach to maximize the benefit for each patient and minimize the treatment-related morbidity.

Before the introduction of curative chemotherapy, definition of limited disease that might be cured by radiotherapy had the highest priority. The availability of a treatment to cure advanced disease has reduced the need for this emphasis on careful staging, and led to a re-examination of the role of staging laparotomy. However, during the 1970s recognition of long-term sequelae of combination chemotherapy, particularly infertility and second malignancies, has led to a reappraisal of its role and careful consideration of the prognostic factors for each patient to allow selection of those who can be cured without risk of late complications.

It is now possible to put together an appraisal of the biological characteristics of Hodgkin's disease, its investigation and its treatment with radiotherapy and combination chemotherapy, and in this book we have attempted to do so. There remain some outstanding questions. The cell of origin of the disease, its precise cause, and its molecular biology are not clear. The choice of treatment, radiotherapy, combination chemotherapy, or combined-modality therapy for some patients, is still controversial. Perhaps the greatest question is that of the further potential for combination chemotherapy. The use of alternative or additional combinations and the development of new salvage therapies continues, but we do not yet know whether we can complete the story of Hodgkin's disease by the introduction of systemic therapy that will cure a greater proportion of patients and not produce acute or chronic complications. The introduction of new biological agents, principally as a result of DNA recombinant technology, and further developments as a result of understanding the molecular biology of the disease remain to be assessed.

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2

Histopathology of Hodgkin's Disease

J.P. SLOANE

Introduction

Hodgkin's disease is an unusual neoplasm, as the malignant cells form only a minority of the tumour mass, the remainder being composed of very variable numbers of lymphocytes, histiocytes, plasma cells, granulocytes, fibroblasts and fibrous tissue. The neoplastic cells take the form of mononuclear Hodgkin cells and multinucleate Reed-Sternberg cells. These are large cells with eosinophilic cytoplasm and often a

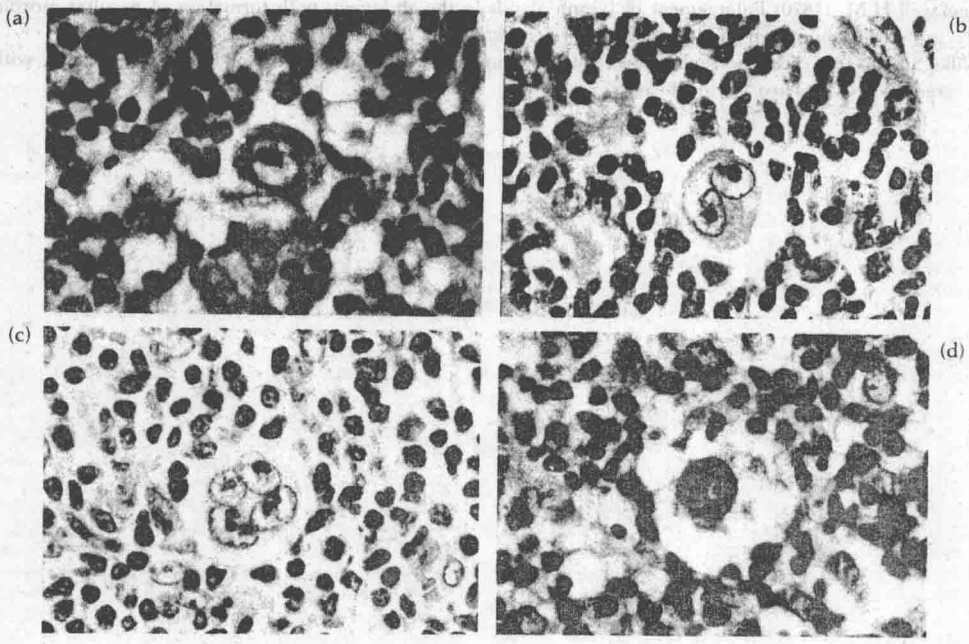

Fig. 2.1 (a) A mononuclear Hodgkin cell. Note the large nucleus, prominent nuclear membrane and inclusion-like nucleolus. (b) Classical binucleate Reed-Sternberg cell with mirror-image nuclei. The nuclear morphology is the same as in (a). (c) Multinucleate Reed-Sternberg cell. (d) Lacunar cell; the nuclei are in a lacuna-like space containing thin wisps of cytoplasm (H & E × 504).

perinuclear halo. The nuclear morphology is striking with a large eosinophilic inclusion-like nucleolus, a thick, well-defined nuclear membrane, and pale-staining chromatin (Fig. 2.1). Although Reed–Sternberg cells classically have two mirror-image nuclei, they frequently contain more than two, and there is often prominent nuclear lobation. It is essential to identify Reed–Sternberg cells in order to make a diagnosis of Hodgkin's disease; mononuclear Hodgkin cells alone are not sufficient. Reed–Sternberg cells are not pathognomonic of Hodgkin's disease, however, and may occasionally be found in other conditions (*see later*). It is therefore necessary to identify them in the correct histological context.

Despite the fact that the neoplastic cells are low in number and often widely dispersed, Hodgkin's disease forms cohesive masses of tissue that infiltrate and replace normal structures, as do other tumours. The lymph nodes are the most frequently involved structures, particularly in the cervical region. Mesenteric nodes and the lymphoid tissue of Waldeyer's ring are rarely involved, however. There is also a tendency for different types of Hodgkin's disease to localize to different nodal groups; mediastinal nodes are commonly infiltrated by nodular sclerosing Hodgkin's disease and high neck and intra-abdominal nodes by mixed-cellularity and lymphocyte-depleted types (Dorfman 1971). Involvement of non-nodal structures, either concomitantly or alone, is discussed later and is usually associated with the nodular sclerosing type (Dorfman 1971). Lymph nodes usually show extensive or complete replacement of architecture by Hodgkin's disease, although occasionally there may be focal infiltration which is usually confined to the perifollicular and interfollicular regions. Colby *et al.* (1981a) described an interfollicular pattern of infiltration in nodes exhibiting follicular hyperplasia where foci of Hodgkin's disease were located between the reactive follicles. This occurred in about 8% of cases.

The Rye classification

Unlike the non-Hodgkin lymphomas, the classification of Hodgkin's disease is widely agreed upon and fairly straightforward. The system in almost universal use is based on that of Lukes and Butler (Lukes *et al.* 1966a, Lukes & Butler 1966) which was modified at the Rye Conference of 1966 (Lukes *et al.* 1966b) and has since become known as the Rye classification. There were six categories in the original Lukes and Butler scheme, namely lymphocytic and/or histiocytic diffuse, lymphocyte and/or histiocyte nodular, mixed type, nodular sclerosis, diffuse fibrosis, and reticular. These became condensed to four at Rye: lymphocytic predominance incorporating the nodular and diffuse variants of lymphocytic and/or histiocytic proliferation, mixed cellularity, nodular sclerosis, and lymphocytic depletion incorporating the diffuse fibrosis and reticular categories.

1 Lymphocytic predominance

This is an uncommon type of Hodgkin's disease and is something of a misnomer, as the predominant cells may be lymphocytes, histiocytes, or both. Eosinophils and plasma

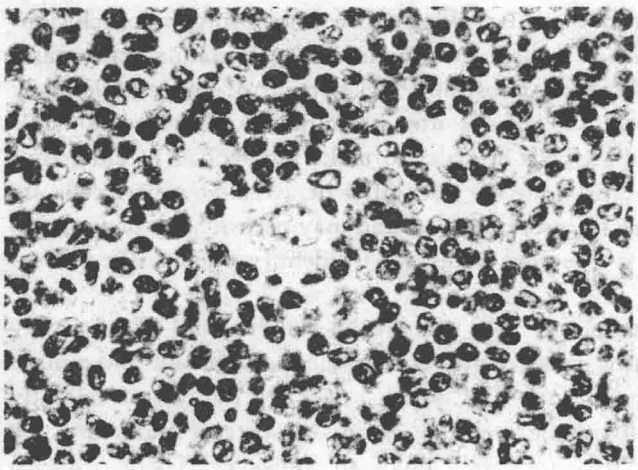

Fig. 2.2 'L and H' cell in a case of lymphocyte-predominant Hodgkin's disease. Compared with the Hodgkin and Reed–Sternberg cells in Fig. 2.1, the cytoplasm is paler, the nuclear membranes thinner and the nucleoli smaller (H & E × 504).

cells are rare, and there is no necrosis or fibrosis. The process usually extends throughout the whole node, but leaving the capsule uninvolved, and may be diffuse or vaguely nodular or both. The nodular lesions are usually predominantly lymphocytic. Characteristic Reed–Sternberg cells are rare; although there was no attempt at enumeration, Lukes and Butler (1966) stated that it may be necessary to search a number of sections in order to find typical cells on which to establish a reliable diagnosis.

There may, however, be large numbers of abnormal, large, polyploid-appearing cells apparently related to Reed–Sternberg cells. These so called 'L and H cells' may account for as much as 10% of the total population. They differ from Reed–Sternberg cells in having pale, rather than eosinophilic or amphophilic, cytoplasm. The nuclei are large and lobated, but the nuclear membranes are thin, the nucleoli usually small, and the chromatin pattern delicate (Fig. 2.2). They are often irregularly distributed and may form small clusters, sometimes in the centre of nodules. They are not regarded as diagnostic of Hodgkin's disease.

Colby *et al.* (1981a) found 'L and H' cells in all cases of lymphocyte-predominant Hodgkin's disease, but they were regarded as prominent in only 18%. They are not exclusive to lymphocytic predominance and may be found in all other subgroups, but are rarely, if ever, prominent.

The reactive histiocytes may form small aggregates or even non-necrotizing granulomata (Fig. 2.3). Langerhans giant cells are not usually seen, however. Colby *et al.* (1981a) found granulomata in almost three-quarters of the cases of lymphocytic predominance, but they were regarded as prominent in only a quarter. Sometimes, the histiocytes may assume an atypical appearance and occur in sheets, leading to an erroneous diagnosis of non-Hodgkin lymphoma.

Immunohistological studies using the *Ulex europaeus* 1 lectin and antisera to factor VIII-related antigen have shown a striking reduction in vascularity in lymphocyte-predominant Hodgkin's disease (Moller & Lennert 1983, Crocker & Smith 1984).

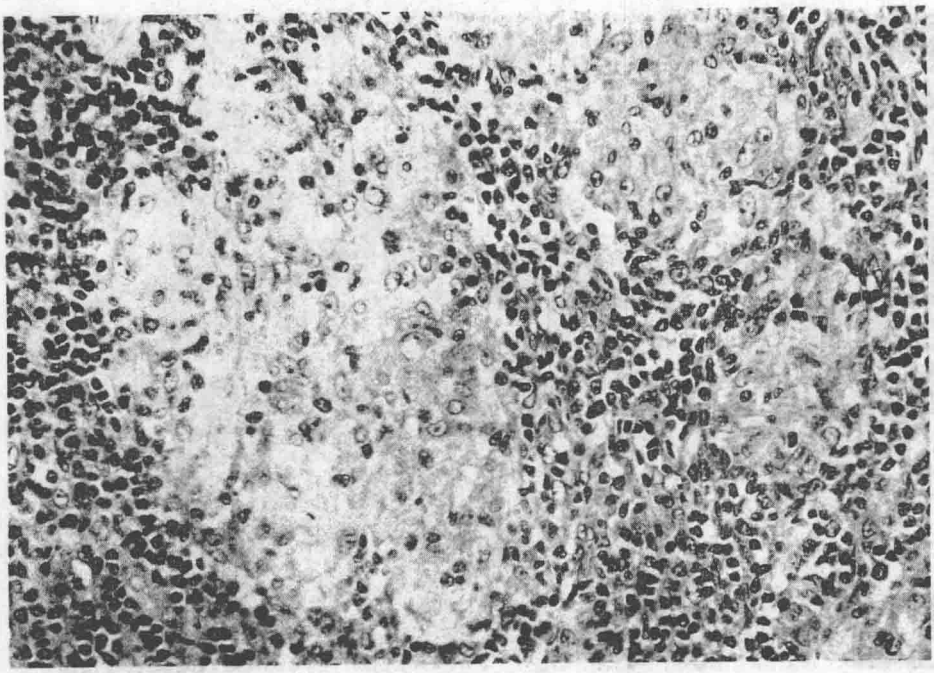

Fig. 2.3 Non-necrotizing granulomata in a lymph node infiltrated by lymphocyte- and histiocyte-predominant Hodgkin's disease. There are no Hodgkin or Reed–Sternberg cells in this field (H & E × 315).

2 Mixed cellularity

This subgroup contains all those cases that lack sclerosis and exhibit too many Reed–Sternberg cells for lymphocytic predominance and too few for lymphocytic depletion. The appearance is therefore very variable. Diagnostic Reed–Sternberg cells are easily identifiable and may be numerous. 'L and H' cells may be identified in some cases but are not prominent. The non-neoplastic cells may include histiocytes, neutrophils, eosinophils, plasma cells and lymphocytes, the numbers varying from case to case and even in different parts of the same section. Granulomata may be identified in over half the cases but are rarely prominent. Foci of necrosis may be seen, and Colby *et al.* (1981a) found these and neutrophils to be related to the occurrence of B symptoms in mixed-cellularity as well as other forms of Hodgkin's disease.

Like lymphocytic predominance, mixed-cellularity Hodgkin's disease is associated with a reduction of nodal blood vessels (Moller & Lennert 1984, Crocker & Smith 1984).

3 Nodular sclerosis

This category is characterized by the presence of interconnecting bands of birefringent collagenous connective tissue surrounding nodules of neoplastic and reactive cells (Fig. 2.4). Capsular thickening is also seen in lymph nodes. The amount of fibrosis is

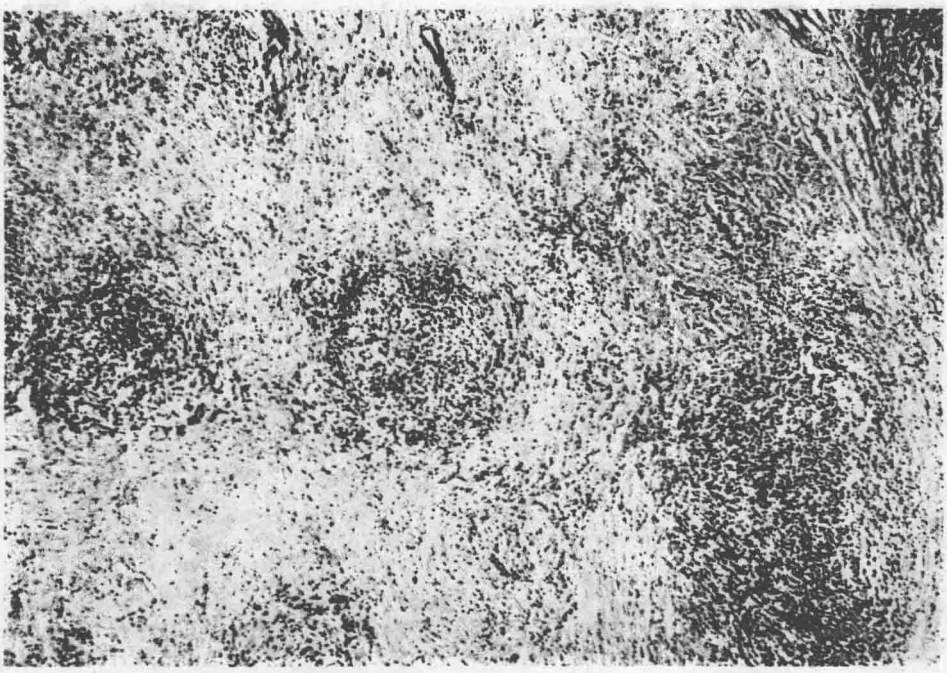

Fig. 2.4 Nodular sclerosing Hodgkin's disease. The fibrosis is very pronounced in this example and divides the neoplastic tissue into nodules of varying size (H & E × 50).

extremely variable not only from case to case but also within the same specimen. The term 'nodular sclerosis, cellular phase' has been used to describe those cases where sclerosis is sparse or absent or may be limited to one portion of the specimen (Lukes *et al.* 1966a). Such patients may have classical nodular sclerosis at other anatomical sites at staging laparotomy (Kadin *et al.* 1971) or in serial biopsies (Strum & Rappaport 1971). An important feature in the recognition of this variant is the presence of clusters of lacunar cells (*see below*) with or without nodularity.

Lacunar cells are variants of Reed–Sternberg cells which have abundant clear cytoplasm and sharply defined cellular borders producing the appearance of a nucleus within a lacuna (Fig. 2.1d). Thin wisps of cytoplasm may extend from the nucleus to the periphery, giving the appearance of a spider's web. The nuclei differ from those of classical Reed–Sternberg cells in having a delicate chromatin pattern and small nucleoli. They are hyperlobated, often with very small lobes. Lacunar cells are characteristic of nodular sclerosing Hodgkin's disease and can be found in virtually all cases, although they are prominent in only 50–60% (Colby *et al.* 1981a). They are not exclusive to nodular sclerosis, however, and may be found in all other subgroups, although rarely in large numbers.

Classical Reed–Sternberg cells are very variable in number and may be sparse; they are, nevertheless, essential for making the diagnosis of Hodgkin's disease. Occasionally, they are present in larger numbers, sometimes forming cohesive clusters with central necrosis. 'L and H' cells are rarely encountered.

This variability in cellular composition has led some workers to subdivide nodular sclerosing Hodgkin's disease according to the content of the nodules. This is usually done using the Rye terminology so that lymphocyte-predominant, mixed-cellularity and lymphocyte-depleted variants are recognized. Bennett *et al.* (1983), however, used a simpler two-grade scheme which was found to be prognostically significant (*see later*). In contrast to other types of Hodgkin's disease, vascularity is increased in nodular sclerosis (Moller & Lennert 1984, Crocker & Smith 1984).

4 Lymphocytic depletion

This comprises two of the original groups of Lukes and Butler, namely diffuse fibrosis and reticular; both patterns may be present in the same specimen.

Lukes *et al.* (1966a) regarded the diffuse fibrosis picture as being the common histological expression of terminal, untreated Hodgkin's disease. There is general cellular depletion, especially of lymphocytes. The accompanying fibrosis varies in appearance and may be loosely cellular, fibrillar, and disorderly, or more cellular and fibroblastic. Sometimes there are hypocellular areas composed of large amounts of amorphous eosinophilic, non-birefringent material. Collagenous bands are not usually seen. Despite the general cellular depletion, there are usually areas where Reed–Sternberg cells are numerous and form the dominant cellular component. Focal necrosis is common in such areas.

In the reticular variant, there is a mixed cellular composition with a numerical preponderance of Reed–Sternberg cells, which may be pleomorphic and 'sarcomatous' in appearance, showing bizarre configurations, nuclear hyperchromatism, giant nucleoli, and extreme nuclear lobation. Necrosis is common.

The diagnostic usefulness of the Rye classification

The Rye classification has gained widespread acceptance amongst pathologists, but, like all other classifications, is not without drawbacks. One problem is that the four groups are not based on the same criteria; three are based on the relative numbers of reactive and Reed–Sternberg cells and the other on the presence of a nodular sclerosing growth pattern. This has led some workers to subdivide the nodular sclerosing group into subcategories according to the content of the nodules (*see below*). Another problem is the uneven distribution of cases between the four groups. Most workers find only small numbers in the lymphocyte-predominant and lymphocyte-depleted categories and a large number of cases in the nodular sclerosing group. Vascular invasion is reported to be of prognostic significance in Hodgkin's disease (Strum *et al.* 1971), but there is no mention of this in the classification.

There have been several studies of observer variation using the Rye classification. Keller *et al.* (1968) and Coppleson *et al.* (1970) each studied variation among three pathologists. Keller *et al.* (1968) found that there was agreement between two out of the three