TUMOURS OF LYMPHOID TISSUE

IN

MILITARY PERSONNEL

by

P.D. STEWART, M.B., Ch.B., Lieutenant Colonel R.A.M.C.

Eastern Command Laboratory

Queen Alexandra Military Hospital, London

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CONTENTS

PREFACE

Most cases of malignant disease in the army are evacuated to The Queen Alexandra Military Hospital for treatment and disposal. A tour of duty at the Eastern Command Laboratory which is responsible for providing the hospital with a pathology service presented the author with an opportunity to review the pathological and some of the clinical findings in cases of tumours of lymphoid tissue in British military personnel and their families, and to assess the importance of these tumours in military medicine.

In addition to describing the clinical and pathological changes found an attempt was made to ascertain the degree of correlation between histology and prognosis and to determine the effect of each tumour on a soldier's military career.

The majority of the patients received treatment at Westminster Hospital and I am grateful to Sir Stanford Cade for permission to study his case notes. Mr. T.M. Prosser, Dr. K.A. Newton and Miss Wheatley of the Radiotherapy Department of Westminster Hospital have also assisted me in many ways.

I am greatly indebted to Dr. G. Lumb who has not only given me much advice and encouragement but has also kindly allowed me to study his material and to Dr. D.H. McKenzie of the Pathology Department of Westminster Hospital for making available certain histological preparations. Several other pathologists throughout the country have sent me sections from biopsies and autopsies and without their help this review would have been more incomplete than it is. I am grateful to Dr. A.H.E. Marshall of the London Hospital for discussing two of the cases of histiocytic medullary reticulosis with me.

When this investigation was begun it was feared that the follow-up of patients might prove very difficult. That this fear was groundless is due entirely to the willing co-operation and assistance I have received from Mr. S. Rosenbaum, Mr. D.T. Beeston and their staff at A.M.D. (Stats.) The War Office; Miss Hedley Prole of the Radiotherapy Department of the Westminster Hospital; Brigadier H.B.F. Dixon of the Ministry of Pensions; numerous civilian clinicians and pathologists; The Army Pensions Office and the officers in charge of records of the units concerned.

I am grateful to the following members of the Royal Army Medical College - Colonel L.R.S. McFarlane for permission to study the material in the Army Tumour Registry, Mr. D.E. Tomkinson for taking all the photographs except two, Mr. R.M. Leech for drawing fig. 1 and Mr. M. Davis, the Librarian, for the many ways in which he has assisted me.

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CHAPTER I

NORMAL LYMPHOID TISSUE AND ITS FUNCTION

Lymphoid tissue (lymphatic nodes, spleen and thymus, etc.) and myeloid tissue (bone marrow) have the same basic architecture and together form the major part of the reticular tissue of the body. Marshall (1956a) has defined the reticular tissue as "a tissue of fixed cells (primitive reticular cells) supported on a framework of fibrils and including all cells in the body derived from this tissue". Primitive multipotent cells and their descendants are not restricted to lymphoid and myeloid tissue, but are also found throughout many organs and tissue e.g. as the sinusoidal cells of the liver and as the peri-vascular primitive cells and histiocytes of connective tissue.

It is neither possible nor desirable to separate reticular tissue into two main independent divisions - lymphoid and myeloid - for not only are these two related histologically but they are often involved together in disease. It has, however, been considered advisable to restrict the scope of the present work to an investigation of tumours which primarily and predominantly involve lymphoid tissue.

A. STRUCTURE OF LYMPHOID TISSUE

It is customary to divide lymphoid tissue into the following categories :-

I. Lymphoid tissue with both afferent and efferent lymphatic vessels - the lymph nodes.

II. Lymphoid tissue with only efferent lymphatic vessels - the sub-epithelial lymphatic nodules of the pharynx, gastro-intestinal tract and respiratory tract. The thymus belongs to this group.

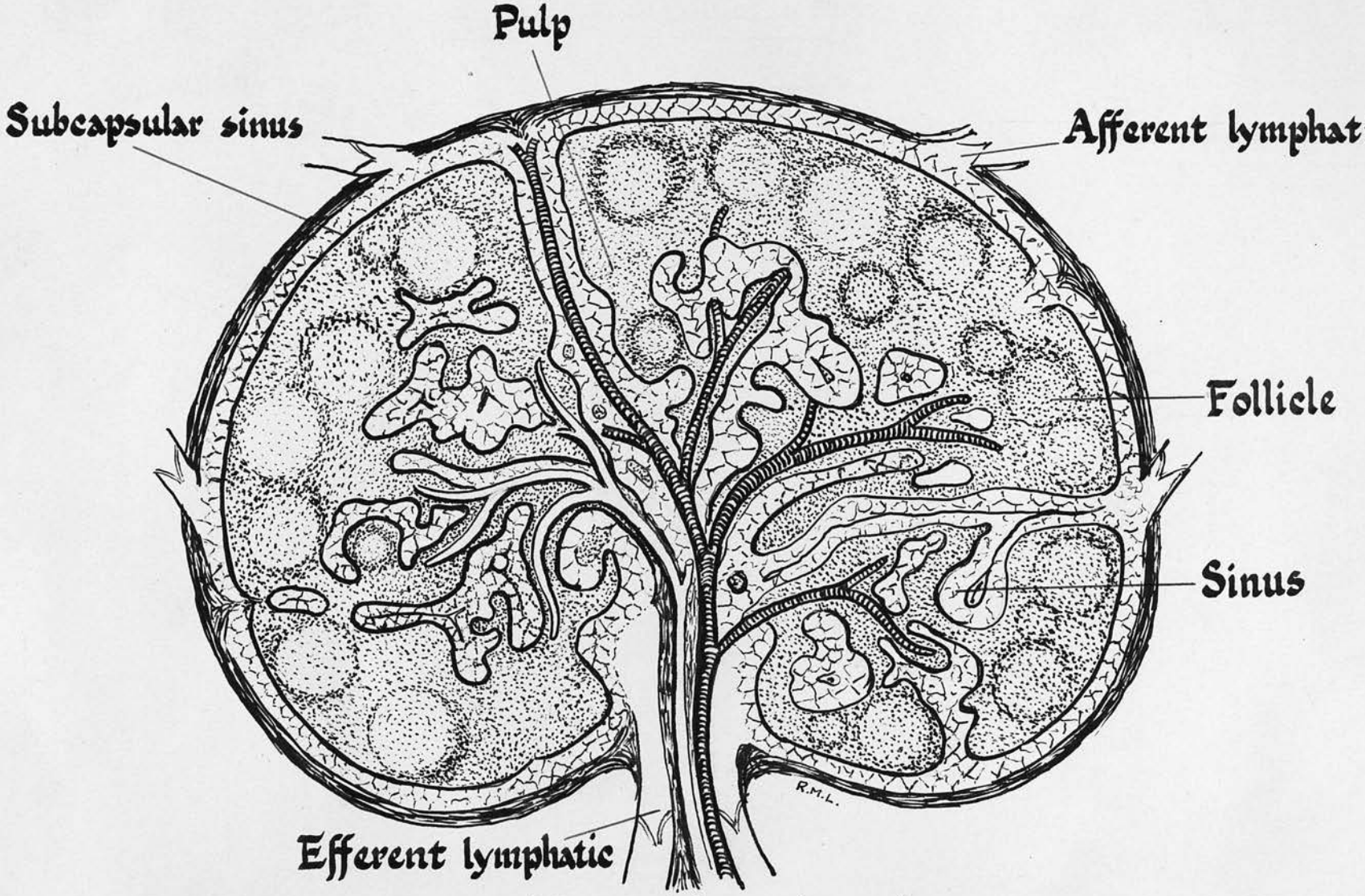


Fig 1. Normal lymph node. (After Heudorfer)

III. Lymphoid tissue with neither afferent nor efferent lymphatic vessels - the lymphoid tissue in spleen and bone marrow.

I. LYMPH NODES

Good descriptions of the structure of a normal lymph node have been given by Robb-Smith (1938), Maximow and Bloom (1942), Lumb (1954) and Marshall (1956a). The general features are shown in fig. 1.

The afferent lymphatics penetrate the fibrous capsule to enter the subcapsular sinus. The subcapsular sinus is drained by sinuses which course through the substance of the gland to the hilum to join the efferent lymphatics. The intranodal sinuses are most prominent in the medullary portion of the gland.

Fine fibrous trabeculae pass from the capsule into the substance of the gland. Reticulin fibres which merge imperceptibly with the collagen of the trabeculae are found in considerable quantity in the pulp and sinus walls but are scanty in the lymphoid follicles (see below). Arteries and veins enter by the hilum and pass along the trabeculae. The capillaries are lined by thickened endothelium which often appears cuboidal in cross section.

The cellular tissue of a lymph node consists of :-

(a) follicles which are found mainly around the periphery. Each follicle has a central arteriole surrounded by a dense collection of lymphocytes. Sometimes the centre of the follicle consists of larger paler staining cells - the so-called germ centre which some authorities regard as abnormal (e.g. Robb-Smith, 1938).

(b) the pulp which is the remaining cellular tissue found between the follicles and in the cords of tissue separating the sinuses (medullary cords). It consists of numerous lymphocytes and reticular tissue with its network of reticulin fibres and associated cells. The pulp is separated from the sinuses by an incomplete sinus wall consisting of special littoral cells and reticular cells. Lymphocytes pass freely into the sinuses.

Anatomically therefore the nodes can be divided into (i) sinuses, (ii) follicles and (iii) the pulp. Harvey et al.(1940) suggested the name lymphon for the unit of lymphoid tissue comprising the cortical follicle with its associated cortical and medullary pulp and sinuses. But the value of this concept which has not been widely adopted has been questioned by Marshall (1956a).

The area of a lymph node around the periphery, containing most of the follicles, is often referred to as the cortex and the remainder as the medulla. It must be remembered, however, that the pulp extends through the cortex and medulla. The division of a gland therefore into cortex and medulla is largely topographical but is useful for descriptive purposes.

The extent of the variations which may be found in the structure of normal lymph nodes in man has not yet been clearly defined as has been done in the case of rats whose lymph nodes Gillman et al.(1952) were able to classify into nine different histological types.

II. LYMPHOID TISSUE WITH EFFERENT LYMPHATICS ONLY

Accumulations of lymphoid tissue are found throughout the pharynx and are particularly prominent as the lymphoid nodules of the

tonsils. Lymphatic nodules also are found in the lamina propria of the stomach, intestine and appendix. In the intestine these lymphatic nodules may extend through the muscularis mucosa into the sub-mucous layer. In the small intestine, especially in the ileum groups of single follicles are fused together to form Peyer's patches. Similar collections of lymphocytes may be found in the sub-epithelial tissues of the respiratory tract.

The thymus comprises a lymphatic element and an epithelial element derived from the third pharyngeal pouch. Involution occurs early and many of the epithelial cells are found grouped together as Hassell's corpuscles.

III. SPLEEN AND BONE MARROW

The spleen is the largest mass of lymphatic tissue in the body. The capsule and the trabeculae consist of dense connective tissue with a number of smooth muscle and elastic fibres. The collagen fibres of the trabeculae are continuous with the reticulin fibres of the pulp. The white pulp which forms a sheath around the arteries has a stroma of reticular tissue the spaces of which are filled with lymphocytes arranged diffusely and in nodules. This white pulp is often referred to as the Malpighian bodies. The red pulp which fills the spaces between the sinuses has a framework of reticular tissue with its reticulin fibres and associated cells. The meshes of this framework are occupied by lymphocytes, free macrophages and elements of the peripheral blood. The sinuses of the spleen are lined by special phagocytic littoral cells and their contents are blood and not lymph. There is still dispute as to whether these sinuses form a closed vascular system or not.

Lymphatic tissue may be found in the bone marrow as focal collections of lymphocytes. (Leitner, 1949; Wintrobe, 1951).

B. HISTOLOGY

A study of the literature on the histology and development of the cells of reticular tissue usually leaves the reader in a state of confusion. Much of this confusion arises from a lack of uniformity in nomenclature. We find what appears to be the same cells described by a wide variety of names and the same name used to designate different cells. Not only are there wide differences in the description of the cells, but there are often divergencies of opinion on the lines of development of the various cells and their potential ability to differentiate into other recognised types.

Modern views on the origin of the cells of lymphoid tissue are based largely on the work of Maximow. Maximow published many papers dealing with the development of mesodermal tissues and much of his work is summarised in the 'Textbook of Histology' published after his death (Maximow and Bloom, 1942), and in two chapters in Cowdry's 'Special Cytology' (1932). He considered that multipotential cells of the embryo were present in the adult and that these cells possessed the property of giving rise to the various mesodermal cells. In lymphoid and myeloid tissue these undifferentiated mesenchymal cells are the primitive reticular cells described below. Even Maximow's writings, however, contain conflicting descriptions and loosely applied terms (Gillman et al, 1949; Marshall, 1953, 1956a).

The basic structure of lymphoid tissue (and of the closely related myeloid tissue) is a supporting framework of reticulin fibres and its associated reticular cells. The exact nature of the reticulin

fibre is uncertain. It is regarded by Mallory and Parker (1927) as a special form of collagen and by Dublin (1946) as a precursor of collagen. Reticulin fibres are frequently continuous with collagen fibres (Nageotte and Guyon, 1930; Maximow and Bloom, 1942).

The cells found in close relation to the reticulin mesh are of two types (Maximow, 1932). The first is the inconspicuous primitive reticular cell with a pale oval nucleus and a cytoplasm which shows little or no phagocytic properties. These cells have indistinct boundaries and exhibit a tendency to form a syncytium around the reticulin fibres. The second cell is the phagocytic reticular cell (fixed macrophage, histiocyte) with a larger paler nucleus containing scanty chromatin and a cytoplasm which is more or less abundant and actively phagocytic.

The distinction between these two types of cells in ordinary histological preparations is not easy but Marshall (1956a) found that they could be separated by silver impregnation; the primitive reticular cells taking up little metal, while the phagocytic cells were metalophil. The primitive reticular cells are the stem cells and all the other cells of lymphoid tissue are derived from them. The descendants of primitive reticular cells are not restricted to lymphoid and myeloid tissue proper, but are found throughout the body - in the liver as Kupffer cells and sinusoidal lining cells and in the connective tissues as macrophages etc.

The lymphatic sinuses of lymph nodes are lined by special fixed phagocytic cells known as littoral cells. These are derived from the primitive reticular cells and like the fixed phagocytic reticular cells can give rise to free macrophages. In the resting

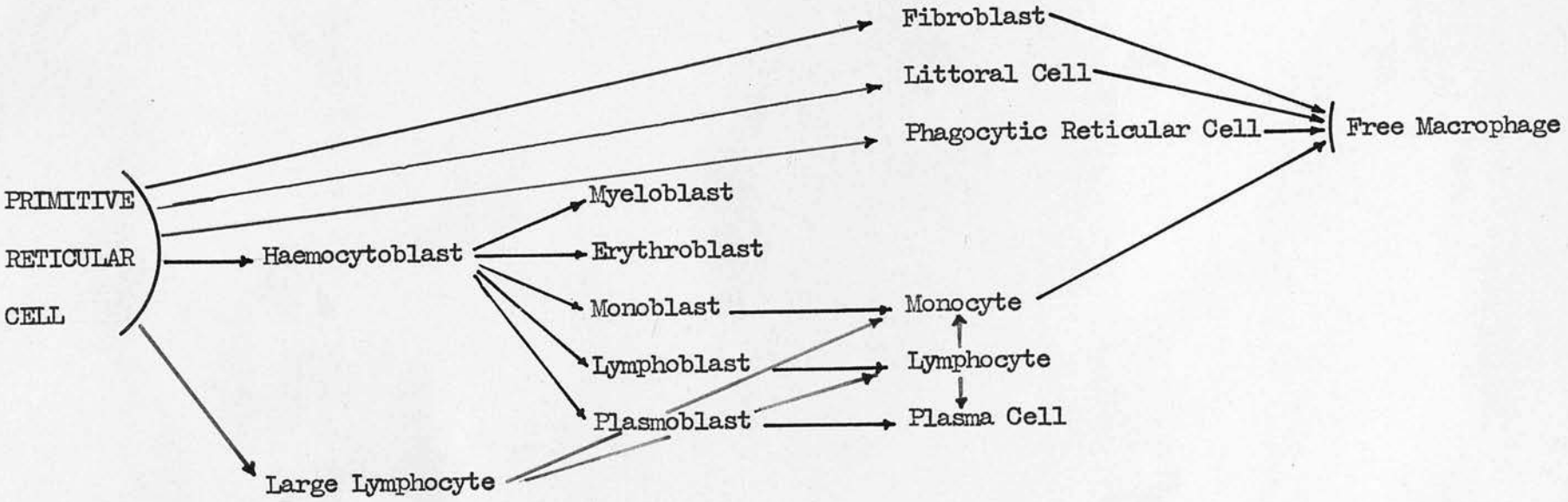
phase the littoral cells are spindle shaped (Robb-Smith, 1938). The nucleus is oval or kidney shaped with inconspicuous nucleolus and the cytoplasm eosinophilic. They phagocytose dye (Cappell,1929) and have an affinity for metals (Robb-Smith, 1938; Marshall, 1953, 1956a) and thus can be clearly distinguished from the endothelium of lymphatic vessels.

The small lymphocyte so common in lymphoid tissue requires no comment. In follicles which are actively producing lymphocytes the central portion may appear paler than the surrounding mass of small lymphocytes on account of the presence of large lymphocytes (lymphoblasts) and a few primitive reticular cells. The nucleus of a large lymphocyte is clear, vesicular and paler than that of the small lymphocyte with its chromatin arranged in nodes in an almost colourless nucleoplasm. Large lymphocytes may also be found in the pulp (Maximow and Bloom, 1942; Robb-Smith, 1938). By mitosis they produce the ordinary lymphocyte. Intermediate forms between the large lymphocyte and the small lymphocyte are also seen.

Also present in lymphoid tissue, especially in the pulp, are plasma cells whose importance is becoming increasingly appreciated. Plasma cells are regarded by some workers as arising from the primitive reticular cell (Marshall, 1956a), while others believe that they can result from the differentiation of lymphocytes (Maximow,1932; Gillman et al., 1949).

Fibroblasts are usually produced from primitive reticular cells direct, but there is also evidence that under certain circumstances they may represent a final stage in the differentiation of the histiocyte (Maximow, 1932).

Fig. 2



DEVELOPMENT OF CELLS OF LYMPHOID TISSUE

Mention must now be made of the "reticulum cell". Although this designation does not appear to have been used by Maximow it is applied by many writers to one or more of the various cells found in lymphoid tissue, particularly to the fixed phagocytic reticular cells but sometimes also to the primitive reticular cells. Marshall (1956a) uses the term "activated reticulum cell" to describe a cell which is not prominent in normal lymphoid tissue but which is commonly found in the follicles of reactive lymph nodes and in reticulum cell sarcoma. These "activated reticulum cells" are larger than the primitive reticular cells and possess a round or oval nucleus composed of fine strands of chromatin with one or two prominent nucleoli. The large, often abnormal, cells with prominent nucleoli seen in some pathological states including Hodgkin's disease and reticulum cell sarcoma are often described as reticulum cells and this use of the term is well established by custom.

A diagram of the general scheme of the development of cells from the primitive reticular cell is given in fig. 2.

C. THE RETICULO-ENDOTHELIUM SYSTEM

Many, but not all, of the cells of reticular tissue possess the property of phagocytosis. By means of vital staining with certain dyes (e.g. trypan blue) and suspensions (e.g. indian ink) these phagocytic cells of reticular tissue can be clearly demonstrated. Cappell (1929) has published in a well illustrated paper an account of the distribution of dye storing cells in the body. These widely scattered cells all possessing the power of phagocytosis were regarded by Aschoff as a functional unity which he designated 'The Reticulo-Endothelial System'. This concept of a reticulo-endothelial system

has proved of value in the study of the defence mechanism of the body. It will be appreciated, however, that this system is not recognisable as an anatomical structure but is a name given collectively to those cells of reticular tissue which are actively phagocytic.

It may be noted that the terms 'macrophage' (Metchnikoff), 'histiocyte' (Kiyono) and 'clasmatocyte' (Ranvier) are sometimes used as synonyms for the fixed and wandering phagocytic cells and sometimes also for the cells lining the sinuses of lymph nodes, spleen and liver.

D. THE FUNCTION OF RETICULAR TISSUE

Lymphoid and myeloid tissue are so closely linked functionally that discussion of one without some mention of the other is neither desirable nor practical. The main functions of reticular tissue are briefly :-

I. BLOOD FORMATION

In the case of lymphoid tissue this consists of the production of lymphocytes. In certain abnormal conditions, however, haemopoeisis may take place in lymphoid tissue.

II. DEFENCE AGAINST INFECTION

(a) By phagocytosis

This is a well established function of the cells of the reticulo-endothelial system (See above).

(b) By formation of antibody

Much experimental work has been carried out in recent years on the production of antibody and this has been well summarized by Wright (1953), Wilson and Miles (1955) and Marshall (1956a). Although it is now considered that antibody is probably produced by

plasma cells, the macrophage cells still have an important function to perform in the initial stages of antibody formation. Antigen injected into an animal is taken up widely by the cells of the reticulo-endothelial system, but the most important localisation is probably in the lymphoid tissue.

III. DISPOSAL OF EFFETE RED CELLS AND BILE PIGMENT AND STORAGE OF IRON

These functions are carried out largely in the spleen, liver and bone marrow.

IV. OTHER METABOLIC FUNCTIONS

These are not yet established but may include participation in lipoid and Vitamin A metabolism.

CHAPTER II

THE CLASSIFICATION OF LYMPHOID TUMOURS

The classification of disease of lymphoid tissue has proved almost as fruitful a source of controversy as the origin and development of the normal cells. Numerous attempts have been made to produce a satisfactory classification of the progressive lymphadenopathies but lack of agreement of views on aetiology, nomenclature and on the origin and relationship of the cells involved has so far prevented the general adoption of any one system. The diseases with which we are primarily concerned are those which are now widely, but not universally, held to be neoplasms.

Hodgkin's disease was the first of the group to be described (Hodgkin, 1832; Wilks, 1856, 1865). As time progressed further clinical and pathological entities were recognised and separated from Hodgkin's disease. In 1846 Virchow described leukaemia and in 1893 Kundrat reported his investigations on a tumour of lymph glands which he distinguished from Hodgkin's disease. Kundrat called this tumour lymphosarcoma thus using the name which Virchow (1864) had previously applied to Hodgkin's disease.

The confusion during this period over nomenclature was not helped by the description, under different names, of conditions which no longer warrant recognition as separate entities. Two of the designations "pseudoleukaemia" and "leukosarcoma" are typical examples from the many which are fortunately no longer used. Pseudoleukaemia was introduced by Cohnheim (1865) to describe a case of what would now be called aleukaemic leukaemia, but use of the term was soon

extended to cover a variety of lymphadenopathies, including Hodgkin's disease, where there were no leukaemic changes in the blood. Sternberg (1905) applied the term leukosarcoma to cases of lymphosarcoma in which there were leukaemic changes in the blood.

At first Hodgkin's disease and lymphosarcoma were considered to be two entirely separate diseases but later workers were struck by certain features which the two processes had in common (Gibbons, 1906; Oliver, 1913; Mallory, 1914; Mueller, 1920; MacCarty, 1930; MacMahon and Parker, 1930; Levin, 1931; Warthin, 1931). Ginsburg (1934) reviewed the conflicting views on the relationship of the two diseases and added his own opinion in favour of their being varieties of the same condition.

The suggestion that Hodgkin's disease might progress to a sarcoma was first made by Yamasaki (1904). Jackson and Parker (1947) considered that Yamasaki's case did not in fact show this change and they regarded the case reported by Welch (1910) as more convincing. The relationship between Hodgkin's disease and Hodgkin's sarcoma is discussed further in Chapter VI.

In 1925 a further disease of lymphoid tissue was recognised and described by Brill et al. (1925) as splenomegalia lymphatica hyperplastica, later to be known as follicular lymphoma, Brill-Symmers disease, etc. At first this disease was regarded as a benign condition but further experience soon showed that at least some cases progressed to a fatal termination often as a lymphosarcoma.

By 1930 Hodgkin's disease and lymphosarcoma were well recognised and in that year and subsequently Roulet (1930, 1932) described a further tumour which differed histologically from lymphosarcoma.

This he called 'Retothelsarkom' now usually referred to as reticulum-cell sarcoma.

Jackson in 1937 drew attention to a type of lymphadenopathy which tended to a benign course, but which he believed sometimes progressed to Hodgkin's disease and for this condition he eventually suggested the term "Hodgkin's paragranuloma" (Jackson and Parker, 1947).

It is with these diseases - Hodgkin's paragranuloma, Hodgkin's disease, Hodgkin's sarcoma, follicular lymphoma, lymphosarcoma and reticulum cell sarcoma, that we are concerned. The recognition of these diseases and the study of their natural history has led to much interest in the possible relationship of one to another.

It is not surprising that attempts were soon made to classify diseases of lymphoid tissue and the allied blood diseases - the luekaemias. The earlier classifications (MacCallum, 1907; Epstein, 1925; Puhr, 1931) have not survived in their original form and one can now appreciate how discerning Adami was when he wrote in 1909 that "Time is not ripe for a full classification of this most complicated group of conditions".

Pullinger (1932) suggested that Maximow's concepts might form a basis for the classification of disease of lymphatic tissue. She suggested the term "Reticulosis" (which she quoted from Letterer) as a suitable word to describe a disease characterized by proliferation of elements of lymphatic tissue, e.g. Hodgkin's disease would be fibro-myeloid reticulosis. Ross (1933) was the first person to suggest an actual classification based on Pullinger's suggestion. This method of classification was further elaborated by Robb-Smith (1938, 1947).

Robb-Smith (1938) defined 'reticulosis' as "a progressive hyperplasia of reticular tissue with differentiation to one or more cell types". His group of reticuloses contained a variety of conditions of different aetiology, including a number of non-specific conditions such as reactive hyperplasia which may have an excellent prognosis. Hodgkin's disease and follicular lymphoma were included in the reticuloses and he drew a clear distinction between the reticuloses and what he regarded as the true malignant tumours of reticular tissues, the reticulo-sarcomata. It was Robb-Smith's hope that some clear relationship would emerge between his various histological types and their clinical behaviour. He has published a further report (Robb-Smith, 1947) giving details of the natural history of his various sub-types. Although Robb-Smith's original hope, that a good correlation between the histological picture and the clinical course would emerge, has not been fully realized (Hadfield and Harrison, 1953), and although his classification is often regarded as over elaborate (Willis, 1948; Tod, 1952; Israëls, 1953), his work nevertheless represents an important contribution to our understanding of the subject.

We have seen how Robb-Smith defined the term 'reticulosis'. Unfortunately this word has become abused and is applied loosely by many writers. As Harrison (1956) pointed out it is often employed to indicate only the progressive fatal diseases of reticular tissue. Both Hadfield and Harrison (1953) and Lumb (1954, 1955) considered that the term, if used at all, should be employed in its widest sense to denote a cellular reaction in reticular tissue.

Robb-Smith's views appear to have made more of an impression in this country than in America as much of the subsequent discussion

and application of his classification has appeared in British literature (Hadfield and Garrod, 1947; Beattie and Dickson, 1943; Bodley Scott, 1948; Marshall, 1956a and others).

Attempts made to classify lymphatic diseases on a clinical or clinico-pathological basis have not met with great success (e.g. Callender, 1934; Forkner, 1937, 1938). Recently Israëls (1953, 1955) has suggested a further clinico-pathological classification which although useful in some respects is probably an over simplification.

The neoplastic nature of all the diseases with which we are concerned has been accepted by a growing body of opinion (Warthin, 1931; Gall and Mallory, 1942; Herbut et al., 1945; Custer and Bernhard, 1948; Willis, 1948; Lumb, 1952, 1954; Harrison, 1956; Evans, 1956 and others). Most modern classifications are based on this view. The term 'Malignant Lymphoma', first used by Minot and Isaacs (1926), was revived by Gall and Mallory (1942) to designate the whole group of primary tumours of lymphoid tissue and this name has attained considerable popularity especially in America.

A number of workers have maintained that, as the nature of at least some members of the group was still uncertain, any designation proposed for the whole group should not connote any aetiology. Krumbhaar (1936) suggested the term 'Lymphomatoid diseases' as being non-committal and preferable to 'Lymphoblastomas' which Mallory (1914) had originally introduced for neoplasms derived from lymphoblasts but which was soon used indiscriminately by others to cover the whole group. Jackson (1937) and Jackson and Parker (1947) simply used the title 'Hodgkin's disease and Allied Disorders' and their classification

which is simple corresponds well with the classifications used by those who consider all the diseases to be true tumours.

Most adherents to the neoplastic theory of these diseases base their histological classifications on Maximow's concept of the development of cells of reticular tissue. They therefore argue that these tumours are all genetically related through the primitive reticular cell, the type of tumour depending on the line of differentiation. Nomenclature and the use of terms vary according to the author's interpretation of the development and inter-relationship of the cells.

The essential unity of the group was stressed by Willis (1948) who emphasised that "the whole group is thus seen as an entity - sarcomas of lymphoid tissue - within which a wide range of structure and behaviour justify, for descriptive and clinical purposes the use of special terms for the main variants". Custer and Bernhard (1948) agreed that "rigid sub-classification of lymphatic tumours is artificial and confusing" and argued that the transitions and combinations which had been reported in the literature (Warthin, 1931; Herbut et al., 1945 and others) and which they have observed "could best be interpreted as indicating a single neoplastic entity having a number of variants". Marshall (1956a) on the other hand has not observed transitions from one type of tumour to another although he noted a tendency for some to become more anaplastic during their course.

Not only have alterations in the type of tumour from one biopsy to another been noted but varying histological appearances have been found in different areas of one tumour (McCartney, 1928; Custer and Bernhard, 1942; Lumb, 1954; Evans, 1956).

We have now reached a stage where the classification of lymphoid tumours would be merely an academic exercise unless it can be shown that the subdivisions proposed give some indication of the likely progress of the disease. All available information confirms that some general predication of the future course can be given from the histological picture although exceptions are not uncommon.

Fortunately the more recently suggested classifications have much in common, even if difference of opinion still exists on the aetiology and inter-relationships of the various diseases. It is now possible to equate fairly satisfactorily the classifications of those authors who regard all the diseases as neoplasms (Gall and Mallory, 1942; Lumb, 1954; Harrison, 1956) with those who are only prepared to accept certain members of the group as true tumours (Parker and Jackson, 1947; Robb-Smith, 1938) - see table I.

Recently a somewhat novel approach to the classification of lymphoid tumours was made by Rappaport et al. (1956). They did not regard follicular lymphoma as an entity and considered that all the malignant lymphomata could be classified as nodular or diffuse according to the architecture of the tumour. They recognised nodular (follicular) and diffuse varieties of the following lymphomata - lymphocytic, well differentiated; lymphocytic, poorly differentiated; mixed (lymphocytic and reticulum cell); reticulum cell and Hodgkin's type.

In probably no other field in oncology is the subject of classification so complicated and confused by the many names employed. It would be of the greatest help to both clinicians and pathologists if, as was advocated by several speakers at the Association of

Clinical Pathologists meeting in October 1956, a standard nomenclature could be agreed upon by an international committee. No doubt advances in our knowledge of the inter-relationship of the cells of reticular tissue and of the tumours arising from these cells, and even changes in our views on aetiology, would necessitate alterations and amendments to any agreed classification from time to time. The possible effect of future developments is not an argument against a beginning being made now.

Table I

Nomenclature of Diseases

Gall and Mallory (1942)	Lumb (1954)	Harrison (1956)	Robb-Smith(1938,1947)[a]	Jackson and Parker (1947)
-	Reticular lymphoma.	Benign Hodgkin's disease.	Lympho-reticular medullary reticulosis.	Hodgkin's paragranuloma.
Hodgkin's lymphoma.	Hodgkin's disease.	Hodgkin's disease.	Fibro-myeloid medullary reticulosis.	Hodgkin's disease.
Hodgkin's sarcoma.	Anaplastic sarcoma of lymphoid tissue (b).	(Not recognised as a separate sub-type).	Polymorphic reticulo-sarcoma (c).	Hodgkin's sarcoma.
Follicular lymphoma	Follicular lymphoma.	Giant follicular lymphoma.	Lymphoid follicular reticulosis.	Giant follicle lymphoma.
Lymphoblastic lymphoma	Lymphosarcoma.	Lymphosarcoma.	Lymphoblastic sarcoma. (reticulo-sarcoma)	Lymphoblastoma (d)
Lymphocytic lymphoma			Lymphosarcoma. (reticulo-sarcoma)	Lymphocytoma (d)
Stem-cell lymphoma	Reticulum-cell sarcoma	Reticulosarcoma.	Syncytial, dictyocytic-syncytial and dictyo-cytic reticulosarcoma (reticulo-sarcoma)	Reticulum-cell sarcoma.
Clasmatocytic lymphoma				

(a) Only the relevant types from this classification are included.
(b) Also includes anaplastic varieties of reticulum cell sarcoma and lymphosarcoma.
(c) "This tumour corresponds with many of the cases of so-called Hodgkin's sarcoma" (Robb-Smith, 1938).
(d) These authors restrict the term "lymphosarcoma" to those cases which present a single invasive and destructive primary tumour.

CHAPTER III

HISTORICAL REVIEW OF LYMPHOID TUMOURS IN THE BRITISH ARMY

The first Annual Report on the Health of the Army covering the year 1859 (Report, 1861) makes no special reference to lymphatic diseases and it is not until the report for 1869 (Report, 1871) that we find listed under the 'Absorbent System' two cases of 'tumour' occurring in 68,962 troops stationed in the United Kingdom. Three further cases were tabulated in the report for 1871 (Report, 1873). In subsequent years there are further entries under the heading first of 'Absorbent System' and then of 'Lymphatic System'.

The first occasion when a definite entity is mentioned is in the report for 1906 (Report, 1907) which contains reference to two patients, out of an average strength of 124,412, being admitted to hospitals in the United Kingdom suffering from Hodgkin's disease. Hodgkin's disease was certainly recognised by medical officers long before this. William Aitken (1872), the first Professor of Pathology at the Army Medical School, in his book on the 'Science and Practice of Medicine' devoted a page to Hodgkin's disease and confessed that in the past he had "aided in the confusion which surrounded the disease". Porter (1878) described two cases of Hodgkin's disease treated in Netley Military Hospital and his paper is illustrated by convincing drawings of the patients. He also mentioned an autopsy which had been performed in 1873 at Netley on a soldier, age 26, where the post mortem findings might have been the result of Hodgkin's disease.

During the first twenty years of the present century occasional cases of Hodgkin's disease were recorded in the annual reports. In the same period a number of papers were published in the Journal of the Royal Army Medical Corps describing cases of Hodgkin's disease and lymphosarcoma (Cotton, 1905; Spencer, 1913; Harrison, 1914; Pollock and Ormrod, 1915; Whittington, 1916; Loughnan, 1919; Abrahams, 1919).

The Medical History of the Great War (Mitchell and Smith, 1931) contains no special reference to Hodgkin's disease or any other of the lymphoid tumours.

Malignant disease received mention in the text, as opposed to the tables, of the annual report for the first time in 1923 (Report, 1925). It was considered that the problem of malignant disease was important although the numbers were small and it was recommended "that a record of the incidence, type and prognosis of such cases as do occur in the army should be carefully recorded". By then histological specimens from tumours were being sent to the Royal Army Medical College and in the next report we find recorded that special attention was being given to the training of pathologists in morbid anatomy especially as regards the accurate diagnosis of tumours (Report, 1926).

Treatment of cancer by deep X-ray therapy and radium is discussed in the 1923 report and in 1925 we find that promising results had been obtained with radiotherapy in several cases of lymphadenoma (Report, 1927).

No annual reports on the health of the army were prepared during the years of World War II but the volume of the official history

of that war dealing with medicine and pathology (Cope, 1952) has been published. Hodgkin's disease receives only passing reference.

Since the last war increasing importance has been attached to the diagnosis and treatment of malignant disease. The two principal post-war developments have been the establishment in 1948 of the Army Tumour Registry at the Royal Army Medical College and the arrangement whereby therapy is given at the Westminster Hospital. These new developments have been recorded in the official reports on the health of the army (Report, 1952, 1953), and described in a paper by Drummond (1949).

The interest of service medical officers in malignant disease in recent years is reflected in the publication of papers which included a report of a case of lymphosarcoma of the mediastinum (Vine, 1946) and a description of five cases of Hodgkin's disease presenting diagnostic problems (Crosby, 1951).

One of the functions of the Army Tumour Registry is to build up a complete and permanent record of tumours in the army by collecting biopsy and autopsy material from all benign and malignant neoplasms. The first report of the Registry covering the years 1948 - 52 has been published (Neal, 1954) and it is obvious, from a study of the tables in this report, that neoplasms of lymphoid tissue form the largest group of malignant tumours in soldiers. Olgilvie (1954) had every justification for stating in his lecture on Ephebiatrics that "Hodgkin's disease, with the other reticuloses, is the commonest manifestation of malignancy in young Service people".

CHAPTER IV

PRESENT INVESTIGATION AND METHODS

Before describing the methods used in the present investigation it is necessary to give a few further details on the management of malignant disease in the army as this has a bearing on the follow-up of cases.

Special arrangements have been made for the treatment of malignant disease of the lung, brain and female genital tract and these do not concern us here. All other cases of diagnosed or suspected malignant disease (including malignant disease of lymphoid tissue) from all military hospitals at home and abroad are transfered to The Queen Alexandra Military Hospital. Biopsy may be performed before or after transfer; if done before, sections either accompany the patient or are available from the Army Tumour Registry. The patients are then seen by Sir Stanford Cade at Westminster Hospital and appropriate treatment begun. During initial periods of treatment the patients normally remain in The Queen Alexandra Military Hospital. Soldiers suffering from malignant disease are, with a few exceptions, unlikely to be fit again for military service. Consequently most cancer patients are eventually discharged from the army and return to their homes throughout the United Kingdom, arrangements having first been made for their medical care at a convenient civilian hospital. Cases running an acute course may, depending on the circumstances, remain in The Queen Alexandra Military Hospital or be transferred to a hospital near their home.

A few military cases of malignant disease are admitted direct to civil hospitals and subsequently transferred to Millbank, unless they are too ill to move.

In planning the present investigation it was decided that it would be unwise to attempt inclusion of cases admitted to hospital prior to 1948, the year in which the Army Tumour Registry was established as there was no guarantee that histological material would be available from earlier cases.

The series therefore consists of all histologically proven cases of lymphoid tumour in British military personnel excluding colonial troops in the period 1948 - 1955 together with the known cases in military families and Chelsea pensioners. The patients are listed in Appendix 1. Cases where on review the histological diagnosis remained in doubt have been excluded as have all cases where the diagnosis was made on clinical grounds only.

Case notes or resumés of case notes in respect of nearly all the British soldiers treated in military and civil hospitals were made available by the War Office. The amount of information recorded on these notes varied from case to case and in some instances details desired for this investigation were lacking.[*] After a soldier's discharge from the army no further medical documents are filed by the War Office. All information relating to subsequent events was obtained through the follow-up department of the Westminster Hospital, or direct from the civilian hospital to which the patient was transferred, or from the patient's doctor. In a few instances where the usual approaches brought no result help was received from the Ministry of Pensions, The Army Pensions Office or the Record Office of the individual's army unit. The problem of

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[*] Occasional deficiences in case notes have necessitated including in some tables an entry showing the number of cases from which the information was tabulated.

tracing missing ex-army cases is especially difficult when they are scattered over the length and breadth of the country.

Histological material was collected from several sources. Blocks from biopsies and autopsies were available from the Army Tumour Registry or from the files of Eastern Command Laboratory. Sections from biopsies and autopsies carried out in civilian hospitals were obtained from the pathologists concerned.

Further cases of lymphoid tumours in Royal Navy, Royal Air Force and civilian personnel treated in military hospitals and in colonial troops admitted to overseas hospitals were also studied during the preparation of this work. A few of these cases are referred to later, but are given separate index numbers preceded by the letter E to distinguish them clearly from the cases of the main series.

In order to gain as complete a picture as possible of the problems involved in the histological diagnosis of the primary lymphoid tumours, it was also necessary to study many preparations from other neoplastic and non-neoplastic diseases of lymph nodes.

Histological sections were stained as a routine by haematoxylin and eosin and by Gordon and Sweets's method for reticulin and when required by Van Gieson's and Ziehl Neelsen's methods. Sections stained by periodic acid, Schiff (P.A.S.) were used in the study of giant cells.

Bone marrow biopsies were examined whenever possible. Almost every case of lymphoid tumour admitted to Millbank during the author's time had a sternal marrow puncture performed. Smears were stained by Leishman and Jenner-Giemsa. Sections were prepared by the

method described by Cappell et al. (1947) and were stained by haematoxylin and eosin, P.A.S. and sometimes by Giemsa.

Electrophoresis of serum proteins was carried out in as many cases as possible from 1954 onwards. The apparatus used was an E.E.L. commercial model and the method employed that of Hughes and French (1956).

In the author's laboratory haemoglobin was estimated by the alkaline haematin method in a photo-electric colorimeter and the erythrocyte sedimentation rate by Wintrobe's technique. Blood grouping was carried out in tubes with two hours incubation; cross matches were set up in saline and in albumin and checked by indirect Coombs's tests. Biochemical estimations were performed by the methods given by King (1951), except for the estimation of total serum proteins which was carried out by Kingsbury's method (Hawk et al., 1947). Details of the methods used in other military laboratories are not known.

The nomenclature of tumours used in this study is given below and is based on the simple and practical classifications of Lumb (1954) and Harrison (1956). Of the types of tumour recognised Hodgkin's sarcoma is the least clearly defined. There is in fact no definite line of distinction between the histological changes of Hodgkin's disease and Hodgkin's sarcoma, the one merging imperceptibly into the other. Nevertheless the term Hodgkin's sarcoma has been retained for those cases at the more malignant end of the histological spectrum, because their recognition has some prognostic value.

Classification of tumours with abbreviations used to identify cases

Tumour	Abbreviation
1. Reticular lymphoma (Lumb, 1954)	RL.
2. Hodgkin's disease	H.
3. Hodgkin's sarcoma	HS.
4. Follicular lymphoma	FL.
5. Lymphosarcoma	LS.
6. Reticulum cell sarcoma	RCS.
7. Mixed cell sarcoma (lymphocytic and reticulum cell)	MCS.
8. Miscellaneous - includes histiocytic medullary reticulosis	Misc.

CHAPTER V

LYMPHOID TUMOURS IN THE BRITISH ARMY 1948-1955

During the period 1948 - 1955 there were 112 histologically proven cases of lymphoid tumours as under :-

Male service personnel	-	106 cases
Female service personnel	-	1 case
Families	-	3 cases
Chelsea Pensioners	-	2 cases

Of the figures given those for families may be incomplete as there is no certain means of tracing any families who may have been treated in civilian hospitals. In the case of service personnel this difficulty does not arise as case notes are preserved in respect of every admission to a military or civilian hospital.

Great caution must be exercised when comparing the present series with most other published series on account of the peculiar age structure of the army with its great preponderance of males of ages 18 - 30. For the same reason some of the conclusions drawn from a study of the present series particularly those relating to the incidence of the various types of tumour, age of onset, etc. apply only to the special population under consideration.

I. CLASSIFICATION

The classification of the 112 cases is shown in table II. The histological type was decided on by the microscopical appearances of the first positive biopsy or of the autopsy material if no biopsy had been performed.

Table II

Classification of Cases

Type	Male	Female	Families	Pensioners	Total
Reticular lymphoma	11				11
Hodgkin's disease	61		1	1	63
Hodgkin's sarcoma	7		1		8
Follicular lymphoma	6				6
Lymphosarcoma	9	1		1	11
Reticulum cell sarcoma	8				8
Mixed cell sarcoma (lymphocytic and reticulum cell)	2				2
Miscellaneous	2		1		3
TOTAL	106	1	3	2	112

It is obvious from table II that Hodgkin's disease is the most common lymphoid tumour in military personnel. This is not surprising. Hodgkin's disease was the most common tumour in many other series (e.g. Gall and Mallory, 1942; Tod, 1952; Lumb, 1954) and is recognised as having a high incidence in the third decade (Jackson and Parker, 1947; Lumb, 1954; Jelliffe and Thomson, 1955).

II. INCIDENCE

The incidence of lymphoid tumours has been calculated only for male and female service personnel (table III) as it was impossible to obtain accurate figures of numbers at risk in the case of families and pensioners.

Table III

Incidence by Years - 107 Cases in Service Males and Females

	Strength	Cases	Cases per 100,000
1948	542,705	15	2.8
1949	404,907	15	3.7
1950	392,233	11	2.8
1951	422,346	12	2.8
1952	446,633	13	2.9
1953	446,182	11	2.4
1954	440,890	14	3.1
1955	423,296	16	3.8
MEAN	439,899	13.4	3.04

The incidence in each major arm of the service is given in table IV. (It is regretted that it is not possible to give the figures on which these calculations are based).

Table IV

Incidence by Arms - 107 Cases in Service Males and Females

Arm		Incidence per 100,000
W.R.A.C. and Q.A.R.A.N.C.	(Female)	1.6
Artillery	Male	2.3
Engineers	Male	2.8
Signals	Male	2.8
Infantry	Male	3.7
Service Corps	Male	2.6
Medical Corps	Male	2.5
Ordnance Corps	Male	3.9
R.E.M.E. (a)	Male	3.2
Boys	Male	3.1
All others	Male	3.2

(a) Royal Electrical and Mechanical Engineers

A comparison with the incidence of lymphoid tumours in the general population is interesting. Robb-Smith (1947) gives a total incidence in Oxfordshire of 45 per million for his types of lymphadenopathy which correspond to the lymphoid tumours of this series - a number which exceeds the highest annual figure (table III) and the highest figure for any one arm of the service (table IV). It is not, however, clear whether the figures of incidence given by Robb-Smith refer to an annual incidence or not. A less reliable comparison can be made with the annual crude death rates for England and Wales from lymphosarcoma, reticulum cell sarcoma and Hodgkin's disease. From 1948 to 1953 these deaths increased from 36 to 44 per million for males, from 18 to 26 per million for females and from 26 to 35 per million for all persons (Registrar General, 1954). Over a period of years the crude death rate can be used as a rough guide to the incidence of these specific tumours because the majority eventually die. With a mean annual incidence of 3.04 per 100,000 troops (30 per million) there is no evidence to suggest that the incidence of lymphoid tumours is higher in the army than in the general population.

Owing to the very small numbers involved the lower incidence of lymphoid tumours in female personnel is in no way significant. Among the male personnel there is no significant difference in incidence in the various arms of the service (table IV).

III. RANK

Nine cases occurred in officers and ninety-eight in other ranks giving a ratio very similar to that of the officer to other rank strength of the army.

IV. SERVICE

It has not been possible to compare the service of patients with lymphoid tumour to that of the army as a whole. There is no obvious suggestion that length of service was of any significance.

V. SERVICE OVERSEAS

This was noted where recorded. It would not appear to be a factor in affecting incidence.

VI. STATION

The strength of the various stations was not available but a study of the locations of the patients does not indicate that the numbers were higher in any one command.

VII. AGE

The age at first admission to hospital of 104 military cases is given in table V. In three instances the age was not recorded. Details of the age structure of the whole army were not readily available but the majority of its personnel were under 30.

Table V

Age First Admission - 104 Serving Personnel

Ages	19[*]	20-29	30-39	40-49	50-59	Total
Reticular lymphoma	5	5		1		11
Hodgkin's disease	20	28	8	2		58
Hodgkin's sarcoma		6	1			7
Follicular lymphoma	3	2	1			6
Lymphosarcoma	6	4				10
Reticulum cell sarcoma	2	4		1	1	8
Mixed cell sarcoma	1			1		2
Miscellaneous		2				2
TOTAL	37	51	10	5	1	104

[*] The youngest age at which boys are enlisted is 15.

VIII. RESULTS

Almost all the cases have been traced until the second half of 1955, the majority until the end of that year. Prognosis is discussed more fully in chapter XIII but table VI gives the consolidated results.

Table VI

Results - All Cases (112)

	Alive	Dead	Total
Reticular lymphoma	9	2 (18%)	11
Hodgkin's disease	28	35 (55%)	63
Hodgkin's sarcoma	-	8 (100%)	8
Follicular lymphoma	5	1 (16%)	6
Lymphosarcoma	2	9 (82%)	11
Reticulum cell sarcoma	1	7 (87%)	8
Mixed cell sarcoma	-	2 (100%)	2
Miscellaneous	-	3 (100%)	3
TOTAL	45	67 (60%)	112

The mortality in eight years was very high in Hodgkin's sarcoma, lymphosarcoma, reticulum cell and mixed cell sarcoma, high in Hodgkin's disease and low in reticular and follicular lymphoma.

CHAPTER VI

THE HODGKIN'S GROUP

In this chapter reticular lymphoma, Hodgkin's disease and Hodgkin's sarcoma will be discussed.

The extensive literature which exists on all aspects of Hodgkin's disease has been well reviewed by Simonds (1926), Walhauser (1933) and Hoster et al. (1948). Many different names have been applied to Hodgkin's disease - Walhauser lists over 50 - but of all the names that have been suggested none is better than the eponymous one.

HISTORICAL

I. HODGKIN'S DISEASE

Hodgkin, who studied at Edinburgh where he graduated, was lecturer in morbid anatomy at Guy's Hospital when in 1832 he published his paper "On some Morbid Appearances of the absorbent Glands and Spleen". In this paper he described seven cases of lymphadenopathy usually with splenomegaly which appeared to be "a primitive affection" of the "absorbent glands" and he distinguished this new disease from "scrofulous inflammation". It is likely, however, that of the seven cases described by Hodgkin, not all were examples of the disease now named after him. Fox (1926) was able to study the surviving material from Hodgkin's original cases and concluded that probably only three would be acceptable nowadays. Naegeli (1932) on the other hand appears to accept all seven.

Hodgkin's paper seems to have attracted no lasting attention at the time. In 1856 Wilks published a paper on "Cases of Lardaceous

Disease and some Allied Affections with Remarks" and in the last paragraph commented on looking for Hodgkin's paper which he found only after completing his own. He felt that Hodgkin's work would have received much wider attention had Hodgkin given the disease which he first described a distinctive name. Wilks classified cases of lardaceous disease into four clinical groups and added a fifth group "Cases of a Peculiar Enlargement of the Lymphatic Glands frequently associated with disease of the Spleen". This last group, he considered, were not strictly examples of lardaceous disease but formed an important fatal condition worthy of separate description, which he proceeded to give, mentioning the enormous size and elastic feel of the glands, the suet like masses in the spleen and the symptoms of "anaemia, prostration and final exhaustion". In a subsequent communication Wilks (1865) further described and defined this disease which he regarded "as separable from lardaceous disease, from cancer and tubercle, although these affections may bear a relation to one another". He again acknowledged Hodgkin's priority and generously suggested the name 'Hodgkin's disease'. In 1878 Wilks yet once more gave credit to Hodgkin.

The next phase in the story of Hodgkin's disease concerns the recognition of the characteristic histological features of the disease which have enabled pathologists to distinguish it from other similar forms of progressive lymphadenopathy. Greenfield (1878) gave a description not only of the naked eye pathology, but also of the microscopical picture as far as was possible with the equipment then available. He noted the presence of multinucleated cells "containing from four to eight or twelve nuclei". It is unfortunate that the

multinucleated cells of Hodgkin's disease are so often referred to as Dorothy Reed cells or Sternberg-Reed cells. Sternberg did not publish his description until 1898 and Reed until 1902. A number of workers have, however, supported Greenfield's claim to priority. although they may not use his name when describing these multinucleated cells. (Beattie and Dickson, 1943; Jackson and Parker, 1947; Symmers, 1948; Mann, 1956).

In 1902 two papers were published which advanced the knowledge of the histology of Hodgkin's disease. Andrewes (1902) reported twenty cases and gave an excellent description of the microscopical findings noting the loss of architecture, the large multinucleated cells, the 'endothelial' proliferation, the fibrosis and in some cases the increase of eosinophils. Reed's (1902) series consisted of eight cases, seven of them boys under seventeen. She described the clinical and pathological findings. The proliferation of 'endothelial' cells, the fibrosis, the capsular thickening, the frequent eosinophil infiltration, the areas of necrosis were all recorded in addition to a description of the multinucleated cells so often named after her. The following year Longcope (1903) published a full account of eight cases and confirmed Reed's findings on the microscopical changes in the lymph nodes. Pullinger (1932) contributed a careful analysis of the histology of thirty-seven cases and gave a useful discussion on the possible histogenesis of the disease which she considered to be "a proliferative process affecting reticulum, and all other cellular manifestations which are recognised as characteristic are due to subsequent differentiation of this one type of cell".

More recent communications have added little to the descriptions of the histology published by Greenfield, Andrewes, Reed, Longcope, and Pullinger.

II. RETICULAR LYMPHOMA AND HODGKIN'S SARCOMA. THEIR RELATION TO HODGKIN'S DISEASE

In 1937 Jackson described a group of cases which resembled Hodgkin's disease but which ran a much more benign course. Some at least of these cases he believed eventually became typical Hodgkin's disease. Histologically the lymph nodes showed diffuse lymphocyte infiltration with scattered multinucleated cells similar to those seen in Hodgkin's disease. Jackson proposed the term "early Hodgkin's disease" for this condition but changed this to Hodgkin's lymphoma (Jackson, 1939) and finally to Hodgkin's paragranuloma (Jackson and Parker, 1944a, 1947). Jackson and Parker (1947) stated that in their experience approximately twenty per cent of these cases progressed to Hodgkin's disease.

Robb-Smith (1947) described under the title 'lympho-reticular medullary reticulosis' a condition very similar to the paragranuloma of Jackson and Parker and although he did not mention progression to Hodgkin's disease, he noted that sarcomatous change may occur after ten to fifteen years. Marshall (1956a) was not certain whether Hodgkin's paragranuloma, which he called 'lymphoid type of Hodgkin's disease', and lympho-reticular medullary reticulosis were the same or not.

Harrison (1952) published an account of six cases which in addition to the histological features noted above, showed a division of the lymph node into lobules by strands of connective tissue. Because of the good prognosis Harrison used the name "benign Hodgkin's disease". None of Harrison's cases had progressed to Hodgkin's disease at the time of reporting, but in a more recent paper he

accepted the possibility of this occurring (Harrison, 1956).

The good prognosis of cases showing the histological picture described above is also stressed by Lumb (1954). In an earlier account Lumb (1952) used the designation 'lympho-reticular lymphoma' but later substituted the simpler term 'reticular lymphoma' (Lumb, 1954, 1955). He regarded reticular lymphoma as a benign form of Hodgkin's disease and represented it in his scheme as a stage further than Hodgkin's disease towards differentiation.

Wright (1956a) examined material from ten cases of paragranuloma. He also found in one hundred and thirty-nine biopsies from cases of Hodgkin's disease fourteen which showed a partial resemblance to paragranuloma. These Wright thought might be regarded as intermediate between the two conditions. Wright was convinced that transitions from paragranuloma to Hodgkin's disease took place and he considered paragranuloma to be a variant of Hodgkin's disease.

Other authors who distinguish between reticular lymphoma (Hodgkin's paragranuloma) and Hodgkin's disease include Bersack (1944), Custer and Bernhard (1948), Peters (1950), Jelliffe and Thomson (1955) and Smetana and Cohen (1956). On the other hand Gall and Mallory (1942), Slaughter and Craver (1942), Tod (1952) and Ackerman (1953) doubt the value of such a distinction.

We have already noted that Yamasaki (1904) and Welch (1910) claimed to have observed the transformation of Hodgkin's disease to sarcoma. That such a transformation can occur is now widely accepted both by those who regard Hodgkin's disease as being a disease of infective or uncertain aetiology (Ewing, 1940; Jackson and Parker, 1947) and by those who consider Hodgkin's disease to be a neoplasm

accepted the possibility of this occurring (Harrison, 1956).

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(Gall and Mallory, 1942; Custer and Bernhard, 1948; Lumb, 1954; Evans, 1956). Some workers, however, have not seen Hodgkin's disease progress to Hodgkin's sarcoma (Robb-Smith, 1956a; Smetana and Cohen, 1956).

There is some difference of opinion on the nature of Hodgkin's sarcoma. Robb-Smith (1938) regards it as a polymorphic reticulosarcoma not directly associated with Hodgkin's disease. Others believe that it merely represents a variant of Hodgkin's disease which runs a rapid course, that there exist every histological gradation between Hodgkin's disease and Hodgkin's sarcoma and that therefore distinction between the two is not warranted (Harrison, 1953, 1956; Ackerman, 1953). Lumb (1954) regards Hodgkin's sarcoma as a type of anaplastic sarcoma of lymphoid tissue and agrees that Hodgkin's disease merges with it.

There is a considerable body of opinion who consider that cases with a histological picture of Hodgkin's sarcoma usually run a rapid downhill course (Gall and Mallory, 1942; Jackson and Parker, 1947; Peters, 1950 ('late stage'); Lumb, 1954 ('anaplastic sarcoma'); Jelliffe and Thomson, 1955 ('Grade 3'); Smetana and Cohen, 1956).

THE AETIOLOGY OF HODGKIN'S DISEASE

The nature of Hodgkin's disease and its aetiology has been the subject of discussion and research for many years and as yet no final answer has been produced. There are two main schools of thought, one maintaining that the disease is an infective process, the other that it is neoplastic. It is well to remember that these two opposing views may in fact not be mutually exclusive (Coley, 1928).

I. INFECTIVE AGENTS

Numerous attempts have been made to incriminate specific micro-organism.

(a) Tuberculosis

It is unfortunate that many of Sternberg's (1898) cases were also suffering from tuberculosis for this led him to conclude that the disease was of a tuberculous nature since he demonstrated tubercle bacilli in the majority of cases. Andrewes (1902), Butlin (1902), Reed (1902), Longcope (1903), Lemon (1924), Uddstromer (1934) all considered, however, that Hodgkin's disease was not a form of tuberculosis although the two may occur together.

Stewart and Doan (1931) found in the serum of patients suffering from Hodgkin's disease high titres of antibody against antigens prepared from extracts of tubercle bacilli, especially of the avian strain. L'Esperance in a series of papers (L'Esperance, 1929a and b, 1930, 1931) reporting the results of culture of material from Hodgkin's disease claimed that the avian strain of the tubercle bacillus was the causal organism. Neither Branch (1931), van Rooyen (1933a), Steiner (1934) nor Jackson and Parker (1947) were able to confirm L'Esperance's claim.

(b) Other organisms

A number of other organisms have been incriminated. Bunting and Yates (1913) isolated a diphtheroid bacillus from a number of cases and suggested that this was the causal organism.

Brucella have been cultured from the blood and lymph nodes of a number of cases of Hodgkin's disease although it was not claimed that these were necessarily the cause of the disease (Wise and Poston, 1940; Poston, 1940; Wise, 1940).

The association of torulosis with Hodgkin's disease has been noted more often than can be accounted for by chance (Gendel et al., 1950; Beck et al., 1955). This may be explained partly by the fact that the lymph nodes in torulosis may present a histological picture strongly suggestive of Hodgkin's disease (Conant et al., 1944) and partly by the fact that patients suffering from Hodgkin's disease are liable to superadded infection with Crytococcus neoformans (Misch, 1955; Levene and Michaels, 1955). In the majority of cases of Hodgkin's disease, no evidence of torulosis can be found.

(c) Virus

It is not surprising that attempts have been made to identify a virus in Hodgkin's disease.

Gordon's (1932, 1933) finding of an encephalogenic agent by the intra-cerebral injection of rabbits with a suspension of Hodgkin's gland in broth and his suggestion that this agent was a virus is well known. Gordon was, however, unable to transmit this agent serially in rabbits. At first it appeared that Gordon's test would be a useful diagnostic procedure as negative results were obtained in other diseases (van Rooyen, 1933b). Later, however, positive results were obtained with bone marrow from a case of myeloid leukaemia and with normal leucocytes, bone marrow and spleen (van Rooyen, 1934, 1937; MacKenzie and van Rooyen, 1935). Further work established that this test was not specific and was probably associated with the eosinophil content of the tissue extracted (McNaught, 1938; King, 1938; Turner et al., 1938). Edwards (1938a and b) concluded that the encephalogenic agent was a constituent of normal cells.

Stewart and Dobson (1924) failed by monkey inoculation to find any evidence of a virus in material from two cases of Hodgkin's disease. By using eggs Lunbäck and Löfgren (1950) claim to have detected virus on two occasions.

Virus like bodies have been reported in the red cells in Hodgkin's disease (Reagan et al., 1954) but later Frajola et al. (1955) demonstrated similar bodies in normal blood.

Bostick (1952) has reviewed the evidence on the possible aetiological importance of viruses in Hodgkin's disease.

II. NEOPLASM

That Hodgkin's disease is held by many to be a neoplasm has already been mentioned. Most of the adherents of the neoplastic theory believe that Hodgkin's disease is a tumour of lymphoid tissue. Medlar (1931), however, considered that Hodgkin's disease was primarily a tumour of bone marrow affecting the megakaryocyte with metastases to lymph nodes. He suggested the name 'Megakaryoblastoma'.

A new approach was made by Thomson (1955, 1956) when he, as a result of a careful study of two hundred and seventy-five cases, concluded that Hodgkin's disease originated as a tumour of the thymus. Hodgkin's disease involving the thymus had been described previously (Symmers, 1924; Rolleston, 1925; Ewing, 1940; Hellwig, 1941) but this was the first time that the thymic origin of most if not all cases of Hodgkin's disease had been postulated.

The aetiology of reticular lymphoma has received less attention. It is usually regarded as a tumour related to Hodgkin's disease.

Study of the present group did not include any new observations on pathogenesis but the impression was formed that the pathological

findings could best be explained by a neoplastic process despite the fact that sometimes the histological picture in Hodgkin's disease was very suggestive of a granuloma.

THE CASES

I. INCIDENCE

The incidence of the Hodgkin's Group is shown in tables VII and VIII. Eighty-two cases were classified as belonging to the Hodgkin's group and these were divided into reticular lymphoma eleven, Hodgkin's disease sixty-three and Hodgkin's sarcoma eight.

Table VII

Incidence of Hodgkin's Group of Tumours in Serving Personnel (excluding families) by years

	Strength	Cases	Cases per 100,000
1948	542,705	10	1.8
1949	404,907	12	3.0
1950	392,233	8	2.0
1951	422,346	8	1.9
1952	446,633	11	2.5
1953	446,182	8	1.8
1954	440,890	11	2.5
1955	423,296	11	2.6
MEAN		79	2.3

Table VIII

Incidence of Hodgkin's Group of Tumours by Arms

Arm		Incidence per 100,000
W.R.A.C. and Q.A.R.A.N.C.	(Female)	Nil
Artillery	(Male)	1.6
Engineers		1.7
Signals		2.4
Infantry		2.4
Service Corps		2.0
Medical Corps		0.8
Ordnance Corps		3.5
R.E.M.E.(a)		2.5
Boys		3.1
All others		2.6

(a) Royal Electrical and Mechanical Engineers

Robb-Smith (1956b) gives the incidence of Hodgkin's disease as 25 per million. The average annual crude death rate for Hodgkin's disease for England and Wales for the years 1948 - 1953 was 22 per million males, 12 per million females and 17 per million all persons (Registrar-General, 1954). When comparing the mean incidence in troops of 2.3 per 100,000 (23 per million) with the figures quoted from Robb-Smith and the Registrar-General it is important to remember that :-

(a) it is possible to use the crude death rates as a rough guide to incidence only because Hodgkin's disease is a fatal condition

(b) it is not known exactly what types of tumour have been included under the term Hodgkin's disease by the Registrar-General

(c) Robb-Smith's figures exclude reticular lymphoma and Hodgkin's sarcoma

(d) Robb-Smith's and the Registrar-General's figures refer to the whole population while the army figures are taken predominantly from an age group in which Hodgkin's disease has its highest incidence.

Accurate comparisons are therefore not possible but taking the above factors into consideration there would appear to be no reason for believing that the Hodgkin's group of tumours is more frequent in the army than in the general population.

The absence of any cases among female personnel is probably due to the small number of women serving, the great majority of the strength of the army being male and to the fact that Hodgkin's disease is commoner in men. The differences in the incidence of Hodgkin's disease in males in the various arms of the service (table VIII) are not significant.

II. HISTORY ON ADMISSION

The symptoms complained of on first admission to hospital were very varied and are given in table IX.

Table IX

Symptoms on Admission

	Reticular lymphoma	Hodgkin's disease	Hodgkin's sarcoma
Total cases	11	63	8
Lump in neck	5	36	2
Lump in axilla	2	12	-
Lump in groin	2	4	1
Pain related to lump	2	4	1
Pain in a limb	-	5	2
Pain in abdomen	-	1	1
Pain in back	-	1	-
Pain in chest	-	4	-
Headache	-	-	2
Gastro-intestinal upset	-	7	1
Cough	-	8	3
Dyspnoea	-	1	-
Haemoptysis	-	1	-
Malaise	-	3	1
Lassitude	-	7	4
Loss of weight	1	4	1
Loss of appetite	1	-	-
Sweating	-	5	-
Temperature	-	2	4
Dark urine	-	-	1
Sore throat	-	1	-
Loss of voice	-	-	1
Itching	-	1	-
Ulcers in mouth	-	1	-
Faint on parade	-	1	-

The protean nature of the presenting symptoms of Hodgkin's disease is well known (Jackson and Parker, 1944c). It will be observed that in reticular lymphoma and Hodgkin's disease the commonest complaint was enlarged glands most often in the neck but in a significant number the axillary glands were complained of. In reticular lymphoma general symptoms were uncommon, whereas in Hodgkin's disease they were commoner and in Hodgkin's sarcoma frequent.

In a number of cases the presence of disease was first detected by some one other than the patient. Two cases were detailed to report sick, one by a sergeant, the other by an officer as they considered the patient looked ill. In three instances the enlarged glands were noted first on a routine medical examination and in no less than six cases the patient's attention was first drawn to the lump by a friend. Five cases were detected as a result of chest X-ray examination; two following routine mass miniature radiography on enlistment and three following chest X-ray on account of cough, haemoptysis and pain respectively.

One case (H18) was known to have been treated for pulmonary tuberculosis several years previously.

The length of time between the first symptom being noted and the first admission to hospital is shown in table X. Sometimes it was almost impossible to decide from the history just when the first symptoms began and this difficulty is a possible source of error in attempting to determine the natural history of these diseases.

Table X

Duration of Symptom before First Admission

	Reticular lymphoma	Hodgkin's disease	Hodgkin's sarcoma
Total cases	10	61	8
Under 1 month	2	23	4
1 - 3 months	2	12	-
3 - 6 months	3	14	2
6 - 12 months	1	5	1
1 - 2 years	1	4	1
2 - 3 years	-	2	-
3 - 4 years	-	1	-
Several years	1	-	-

Cunningham (1915) found that the time between the first signs of disease being noted and consultation varied from a few weeks to ten years with an average of ten months.

It reflects credit on unit medical officers as a whole that the interval between the soldier first reporting sick in his unit and his admission to hospital was usually about one to two weeks although in a few instances the period was longer - up to six months. That a few cases should be under somewhat lengthy observation before admission is, perhaps, not surprising in a group of diseases with such a variable and often insidious onset.

II. CONDITION ON FIRST ADMISSION

(a) Lymphadenopathy

The extent of superficial lymphadenopathy on first admission is given in table XI.

The glands in reticular lymphoma were usually mobile, painless often firm but sometimes gave the impression of being cystic or fluctuant. In one case the glands were mobile, rubbery and tender.

In Hodgkin's disease the glands were often found to conform to the classical description of non-tender, firm, rubbery, discrete, mobile glands occurring in masses, but a number of variations were noted - a few were tender, a few hard, a few almost fluctuant, and a few partially matted.

The glands in cases of Hodgkin's sarcoma presenting with lymphadenopathy were not obviously different from those of Hodgkin's disease.

Table XI

Superficial Lymphadenopathy on First Admission

	Reticular lymphoma		Hodgkin's disease		Hodgkin's sarcoma	
Total cases	10		63		8	
Restricted to one side of neck	4	7	18	23	2	2
Restricted to one axilla	2		5		-	
Restricted to one groin	1		-		-	
Two or more regions involved	3		33		2	
No superficial nodes	-		7		4	

It is interesting to note the sites of enlarged superficial glands in the cases of Hodgkin's disease (table XII).

Table XII

Superficial Lymphadenopathy in

56 cases of Hodgkin's Disease on First Admission

Left cervical	-	35 cases
Right cervical	-	33 cases
Left axillary	-	17 cases
Right axillary	-	22 cases
Left groin	-	5 cases
Right groin	-	6 cases

The number of cases with axillary lymph node enlargement is striking and is higher than that recorded by Jackson and Parker (1945b, 1947).

(b) Enlargement of Mediastinal Shadow on X-ray

In ten out of the eleven cases of reticular lymphoma the chest X-ray was normal; in the eleventh (RL. 4) no early X-ray report was available. In the cases of Hodgkin's disease twenty-four out of the sixty-three had enlargement of the mediastinal shadow on first admission but this was found in only one out of the eight cases of Hodgkin's sarcoma. Where further detail was given it usually recorded the enlargement as being in the anterior mediastinum.

In five cases of Hodgkin's disease (all discovered by X-ray examination) mediastinal glandular enlargement was present without superficial lymphadenopathy. Such a finding was rare in the

experience of Jackson and Parker (1945a) and Goldman and Victor (1945) and may be accounted for partly by the increased use of mass miniature radiography. The diagnosis in four of these cases was only established after thoracotomy; in the fifth the development of a cervical mass provided a more accessible biopsy.

(c) Enlargement of Spleen and Liver and Presence of Abdominal Masses

The incidence of clinically enlarged liver and spleen, and of abdominal masses which were thought to be enlarged lymph nodes is given in table XIII.

Table XIII

Abdominal Signs

	Reticular lymphoma	Hodgkin's disease	Hodgkin's sarcoma
Cases	10	63	8
Splenomegaly	0	10	1
Hepatomegaly	1	1	0
Abdominal mass	0	4	1

(d) General Condition

Constitutional manifestations were recorded on admission in only one case of reticular lymphoma (RL. 7), in twenty-two cases of Hodgkin's disease and in seven cases of Hodgkin's sarcoma.

One case of reticular lymphoma (RL. 7), sixteen cases of Hodgkin's disease and three cases of Hodgkin's sarcoma were febrile on admission. Two of the patients with Hodgkin's sarcoma were jaundiced.

(e) Other Observations

One case of Hodgkin's sarcoma was found to have a tumour of the nasopharynx. Radiological evidence of involvement of lung as well as the mediastinum was present in one case of Hodgkin's disease and one case of Hodgkin's sarcoma.

(f) Blood and Bone Marrow

This is discussed under Laboratory Investigations (Chapter X).

III. COURSE OF DISEASE

It has been found impossible to present a detailed account of events occurring during the course of these diseases, owing to the incompleteness of the available information relating to the subsequent progress of some of the cases, especially after their discharge from the army. Where figures are given they cover only recorded observations: the real incidence may be higher.

(a) General

In no less than seven of the cases of reticular lymphoma no further extension of the disease was detected. Two cases (RL. 2 and RL. 4) progressed to Hodgkin's disease. One (RL. 7) died after an illness lasting less than one year.

In Hodgkin's disease progression after a variable interval was the rule although a few exceptions were noted (e.g. case H.26). All the cases of Hodgkin's sarcoma ran a rapid downhill course.

(b) Extension of Lymphadenopathy

Extension to further groups of superficial glands was seen in three of the cases of reticular lymphoma.

The appearance of further groups of enlarged glands was a common finding in the course of Hodgkin's disease and this extension

of lymphadenopathy was liable to affect any glandular region, including the abdomen and thorax. In Hodgkin's sarcoma the development of superficial glands or the extension to previously unaffected groups was common.

(c) Enlargement of the Mediastinal Shadow on X-ray

This was noted only once in reticular lymphoma but was recorded as occurring in five cases of Hodgkin's disease and one case of Hodgkin's sarcoma.

Thus enlargement of the mediastinal shadow was a very common feature in Hodgkin's disease being present in twenty-four cases on admission and developing at a later stage in at least another five patients out of a total of sixty-three cases. The frequency of involvement of the mediastinum has often been remarked on (Peirce et al., 1936; Wright, 1938; Baker and Mann, 1940; Wolpaw et al., 1944; Goldman and Victor, 1945). Thomson (1956) stressed this feature as an argument in favour of the thymic origin of Hodgkin's disease.

(d) Enlargement of Spleen and Liver

Splenomegaly appeared in two cases of reticular lymphoma, in nineteen cases of Hodgkin's disease and in three cases of Hodgkin's sarcoma. Taking into account also the cases with enlarged spleen on admission (table XIII), splenomegaly becomes a frequent finding. Enlargement of the liver was less frequently seen, but was by no means uncommon.

(e) Involvement of Lung

This was noted as a development in six cases of Hodgkin's disease and one of Hodgkin's sarcoma.

(f) Involvement of Bone

In one case of reticular lymphoma (RL. 4) and in eight cases of Hodgkin's disease there was clinical evidence of extension of the disease to bone, often the spine. The real incidence of bone involvement in Hodgkin's disease is certainly higher than the clinical and radiological findings would lead one to suspect (Steiner, 1943; Griffiths, 1955).

(g) Skin Manifestations

Skin manifestations were noted in one case of reticular lymphoma, in one case of Hodgkin's sarcoma and in sixteen cases of Hodgkin's disease.

In Hodgkin's disease skin lesions were often of a non-specific character taking the form of prurigo. In one case an infiltrative lesion appeared in the skin (H. 39) in another (H. 31) underlying tumour broke through the skin surface to create two large ulcers. The occurrence of herpes zoster in four cases is discussed below.

(h) Involvement of Nervous System

We have already noted (table IX) that a number of patients with Hodgkin's disease on admission complained of pain in one or other limb or across the back. Several other patients developed a similar type of pain during the course of their disease. It is generally thought that such pain is caused by enlarged glands pressing on spinal roots or peripheral nerves.

Of the Hodgkin's disease patients one developed definite sensory loss in the distribution of the ulnar nerve, another evidence of pressure on the spinal cord and a third died with signs which might have been due to a cerebral deposit possibly in the frontal

region. It is unfortunate that no autopsy was performed in the last case for true cerebral as opposed to meningeal deposits are very rare in Hodgkin's disease (Fein and Newill, 1954).

The occurrence of four cases of herpes zoster in the sixty-three cases of Hodgkin's disease is more than a coincidence. Rolleston (1925) considered that herpes zoster was frequent in Hodgkin's disease and Conybeare (1933) records three instances in a series of thirty-five cases. It has been suggested that the herpes may be associated with peri-neural extension of the disease and involvement of nerve ganglia (Goldman, 1940; Goldman and Victor, 1945; Lever, 1954). Whatever the explanation it is interesting to speculate whether the increased incidence of herpes zoster in Hodgkin's disease and the appearance of skin and breast carcinoma after herpes (Wyburn-Mason, 1955) could in any way be related.

One case of Hodgkin's sarcoma (HS. 2) developed inco-ordination of hands and feet and typical cerebellar speech before death, but no autopsy was performed.

(j) Pyrexia

Pyrexia was a common feature in the Hodgkin's group except in reticular lymphoma. The pyrexia was

(i) irregular, continued, or remittent.

(ii) relapsing in which the temperature gradually rose over a period of days to 104°F or even higher and then after a further few days gradually returned to normal or near normal to be followed after an interval by similar episodes. The duration of the pyrexial periods and intervals was variable. This type of fever is usually referred to as Pel-Ebstein fever after Pel (1887) and Ebstein (1887)

although it was clearly recognised much earlier by Murchison (1870) and mentioned by Greenfield (1878). It has been the subject of special study by MacNalty (1911, 1928).

Table XIV shows the number of cases in which pyrexia was recorded.

Table XIV

Pyrexia in Hodgkin's Group

	Cases	Pel-Ebstein	Other Types	Total
Reticular lymphoma	11	1 (a)	1	2
Hodgkin's disease	63	13	18	31
Hodgkin's sarcoma	8	3	3	6
TOTAL	82	17	22	39

(a) After progression to Hodgkin's disease

There was a definite tendency in our cases for subjective symptoms to become worse and for physical signs to become more prominent during pyrexial periods of Pel-Ebstein fever.

(k) Other Manifestations developing during the course of disease

Jaundice appeared in eight cases of Hodgkin's disease and in two cases of Hodgkin's sarcoma. Pleural effusions and ascites were seen in both Hodgkin's disease and Hodgkin's sarcoma. Gastro-intestinal symptoms occurred in a few instances. Signs of cardiac failure supervened towards the end in several cases. Epistaxis, haematemesis, petechial and purpuric eruptions were noted in cases of Hodgkin's sarcoma. One case of Hodgkin's sarcoma (HS. 1)

developed symptoms and signs of an abdominal perforation before death.

(1) General Comments

The complications recorded above as being seen in reticular lymphoma occurred almost entirely in three cases (RL. 2 and RL. 4 who progressed to Hodgkin's disease and RL. 7 who died after a short illness).

PATHOLOGY

It is not proposed to describe in detail the histological features of all three diseases but rather to note a number of points which have emerged from a study of the available biopsy and autopsy material and to compare some of these with previously recorded findings.

A. BIOPSY

I. RETICULAR LYMPHOMA (Syn. Hodgkin's paragranuloma)

The first biopsy (and in eight cases the only one) showed the histological picture of reticular lymphoma in all eleven cases.

The lymph nodes were moderately enlarged (up to 4.5 cms. in length), smooth, firm, often slightly lobulated and presented a homogeneous greyish-white cut surface.

Microscopically the capsule was intact. In three instances it was still possible to discern peripheral follicles in parts of the section but in the remainder the architecture was completely destroyed. Harrison (1952) noted this occasional persistence of normal tissue at the edge and Smetana and Cohen (1956) stated that obliteration of architecture was whole or partial. Division of the gland into

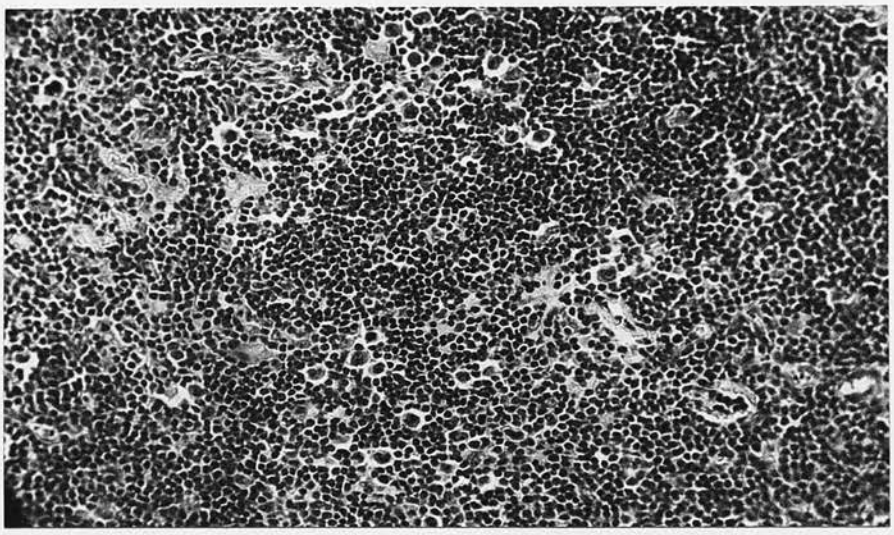

Fig. 3. Reticular lymphoma (RL. 3). Lymph node. Lymphocytes with scattered reticulum cells. (H. & E. X 110).

lobules by bands of collagen or reticulin was seen in eight instances but was not a prominent feature. Harrison (1952) stressed this lobulation and Lumb (1954) found it a frequent feature in reticular lymphoma, but most of Wright's(1956) sections showed little or no fibrosis.

All sections demonstrated the characteristic lymphocytic infiltration with scattered single abnormal reticulum cells many of which were multinucleated (fig. 3). The number of abnormal reticulum cells varied from case to case. Eosinophils were seen in only one section and then in scanty numbers. A few plasma cells were also present in one case. Jackson and Parker (1944b, 1947) found plasma cells to be not uncommon and sometimes numerous, but in Harrison's (1952) cases they were scanty.

Mitotic figures were seen in five out of the eleven cases but never in large numbers. Areas of necrosis such as are sometimes found in Hodgkin's disease were not present.

In two instances (RL. 2 and RL. 4) repeat biopsies taken seven and four years respectively after the first biopsy, showed typical Hodgkin's disease. Case RL. 2 is still under observation; case RL. 4 subsequently died - but no autopsy was performed. A further example of transition from reticular lymphoma to Hodgkin's disease was seen in an R.A.F. patient not included in this series (RL.E3). A post mortem was performed on this additional case and the histological picture at autopsy showed further progression towards Hodgkin's sarcoma.

One case (RL. 7) ran a rapid downhill course and died within one year; yet a lymph node biopsy taken soon after his first admission to hospital can only be classified histologically as

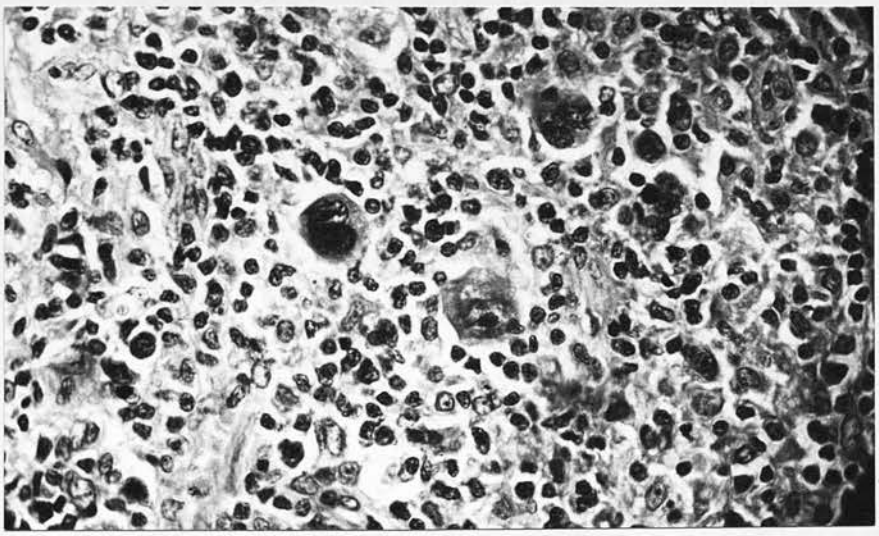

Fig. 4. Hodgkin's disease (H. 22). Lymph node. Typical giant cells. (H. & E. X 330).

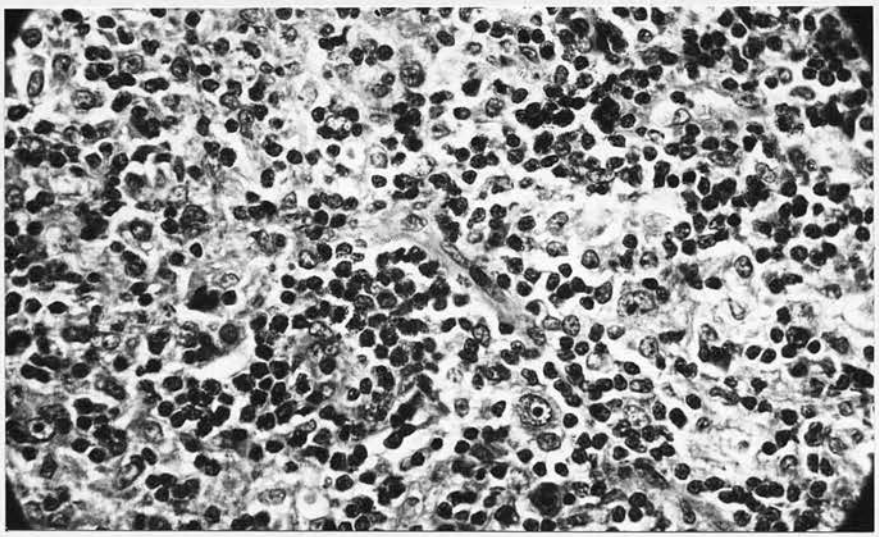

Fig. 5. Hodgkin's disease (H. 22). Lymph node. Another field from same section as Fig. 4 to show reticulum cells, lymphocytes and eosinophils. (H. & E. X 330).

reticular lymphoma. A second gland biopsy carried out two months afterwards showed chronic lymphadenitis. It is not easy to explain this case. Reticular lymphoma may be confused histologically with lymphosarcoma (Harrison, 1956) but in the material available there is little evidence to support the latter diagnosis. It is more likely that this case had already progressed to Hodgkin's disease, lymphosarcoma or reticulum cell sarcoma when first seen and that the glands removed by biopsy were not yet involved in the change. Attention has already been drawn to the fact that the histological picture in lymph nodes may vary from gland to gland. It is unfortunate that permission for autopsy was refused.

II. HODGKIN'S DISEASE

In all seventy biopsy specimens were available from the sixty-three cases. The biopsy sites were :-

Cervical nodes	-	47	
Axillary nodes	-	8	
Inguinal nodes	-	2	62
Mediastinal nodes	-	3	
Abdominal nodes	-	2	
Other sites	-	8	
TOTAL		70	

Macroscopically biopsy lymph nodes were moderately enlarged, encapsulated and easily separated from each other. They were usually firm, but not hard and presented a homogeneous greyish-white cut surface, except in a few cases where the surface was intersected by slightly depressed denser bands of fibrous tissue.

Although complete destruction of the normal lymph node architecture was usual in no less than sixteen of the biopsies it

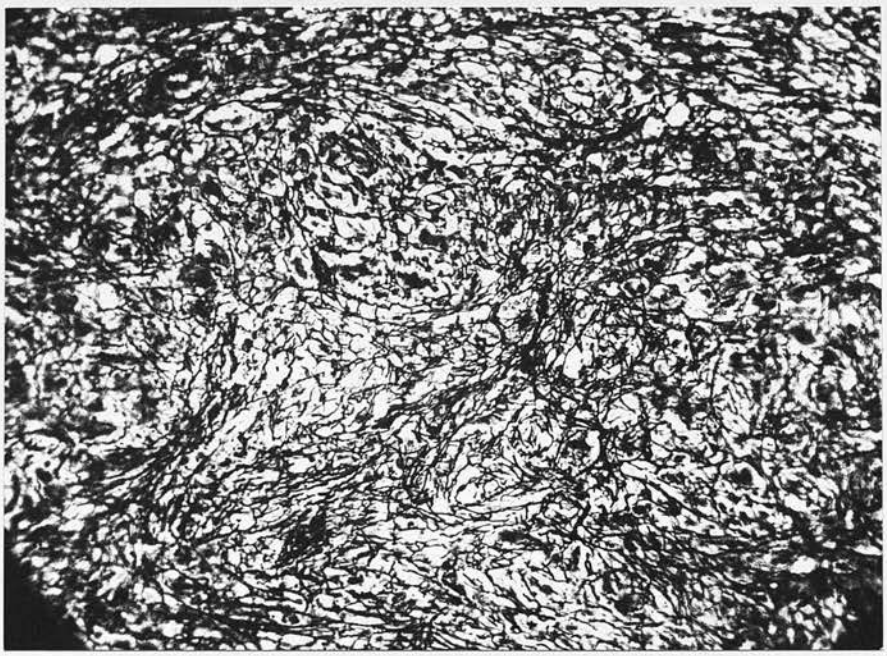

Fig. 6. Hodgkin's disease (H. 12). Lymph node. Increase in reticulin fibres. (Gordon and Sweets X 110).

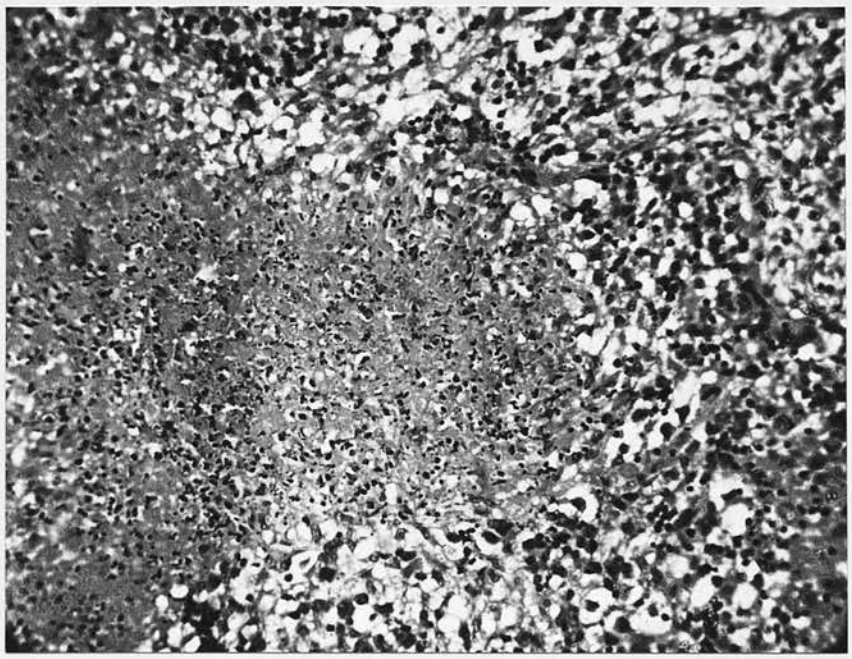

Fig. 7. Hodgkin's disease (H. 38). Lymph node. Necrotic area with degenerate polymorphs. (H. & E. X 110).

was still possible to identify remaining relatively normal tissue in areas, often around the cortex.

The capsule was thickened in many cases and was infiltrated in six. Obvious penetration and involvement of the periglandular structure was not seen. There has been a considerable divergence of opinion on capsular invasion in Hodgkin's disease; but Gibbons (1906), Oliver (1913), Ginsburg (1934), MacCallum (1940) and Jackson and Parker (1947) all state that it may occur.

Fibrosis, a very common finding, varied from small tortuous strands of collagen scattered throughout the gland to broad bands intersecting the gland and surrounding more cellular areas. Hyalinisation of the collagen was frequently seen. Fibrosis was so common and sometimes so marked even in biopsies taken early in the disease before treatment, that it must be regarded as an integral part of the pathological process in Hodgkin's disease. Fibroblasts were frequently present and in one biopsy were so numerous as to give a quite unusual histological picture.

Reticulum fibrils were usually present in increased numbers, (fig. 6).

Areas of necrosis usually with polymorph infiltration are a well recognised feature of Hodgkin's disease (Reed, 1902; Pullinger, 1932; Mills and Pritchard, 1935). Five lymph node biopsies showed such necrotic areas (fig. 7). These areas varied in size but were usually small.

The characteristic pleomorphic cellular proliferation (figs. 4, 5) always included lymphocytes and abnormal reticulum cells. The abnormal reticulum cells are large cells with irregular outlines

and large vesicular nuclei containing a prominent eosinophilic nucleolus. In addition multi-lobed and multinucleated forms - the so-called Sternberg-Reed giant cells - were always found. The nuclei of the giant cells were arranged in a variety of ways among which mirror image and horse-shoe patterns were frequently seen. The numbers of lymphocytes to abnormal reticulum cells varied considerably as did their spatial relationship one to another. In most glands they were irregularly mixed, in some there was a tendency for the reticulum cells to form aggregates surrounded by lymphocytes, and in one the reticulum cells were arranged round the periphery of focal collections of lymphocytes.

The tendency for reticulum cells to show vacuolation of their cytoplasm and thus to present an appearance of lying in gaps or holes (Lumb, 1954) was noted in several sections and was a useful diagnostic feature.

Multinucleated cells, which are essential to a diagnosis of Hodgkin's disease (Pullinger, 1932; Jackson and Parker, 1947; Smetana and Cohen, 1956 and others), were sometimes scanty, more often present in moderate numbers and occasionally abundant. Erythrophagocytosis in multinucleated cells was noted once.

Eosinophils were usually seen; in only twelve biopsies were none found. They varied from scanty to very numerous. Their distribution even in a single section was often irregular; in a few instances they were arranged in focal aggregates. Many of these eosinophils possessed a single round nucleus - a feature noted by Pullinger (1932) but seen rarely by Longcope (1903). In eighteen of our cases(including some cases not in the main series) a peripheral

blood count and bone marrow biopsy were performed about the same time as the gland biopsy. Blood eosinophilia and proliferation of eosinophil myelocytes in the marrow were infrequent and bore no constant relationship to tissue eosinophilia (see table XV).

Table XV

Eosinophilia in Blood, Marrow and Tissue

Case No.	Blood	Marrow	Tissue
H. 8	Nil.	Nil.	Marked
H. 11	Slight	Nil.	Marked
H. 14	Nil.	Nil.	Nil.
H. 17	Nil.	Nil.	Slight
H. 22	Nil.	Nil.	Marked
H. 25	Nil.	Nil.	Marked
H. 35	Nil.	Marked	Marked
H. 38	Slight	Slight	Marked
H. 41	Nil.	Nil.	Slight
H. 48	Nil.	Nil.	Slight
H. 51	Nil.	Nil.	Slight
H. 61	Nil.	Nil.	Marked
H. 63	Nil.	Nil.	Moderate
H. E1	Nil.	Nil.	Marked
H. E2	Nil.	Nil.	Marked
H. E3	Nil.	Slight	Marked
H. E4	Nil.	Nil.	Marked
H. E5	Nil.	Nil.	Marked

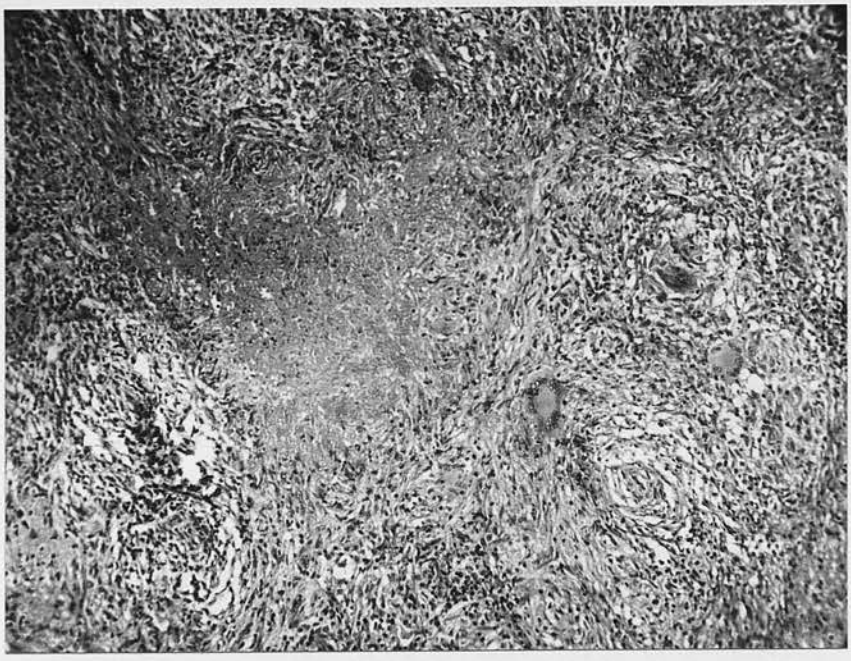

Fig. 8. Hodgkin's disease and tuberculosis (H. 36). Lymph node. Area of caseating tuberculosis. (H. & E. X 55).

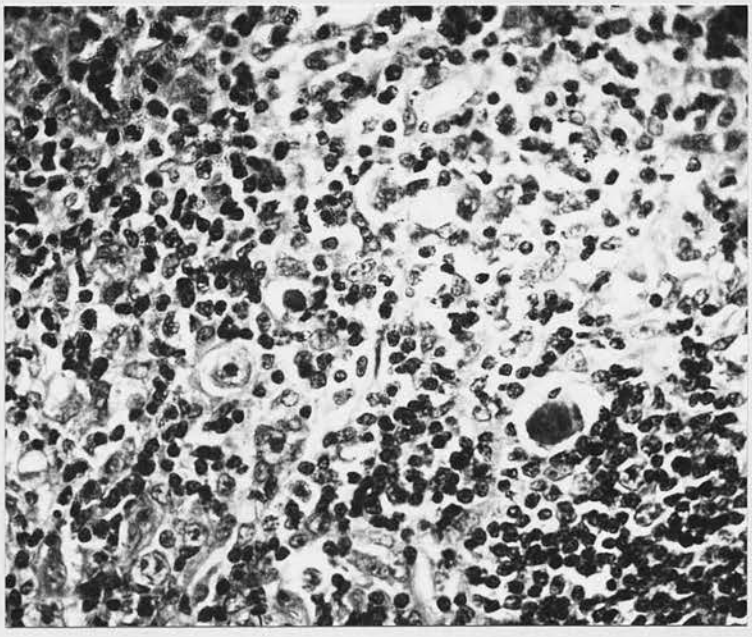

Fig. 9. Hodgkin's disease and tuberculosis (H. 36). Lymph node. Same section as Fig. 8. Area of Hodgkin's disease with giant cell. (H. & E. X 330).

This lack of eosinophilia in the marrow and blood together with the frequent presence in biopsy sections of eosinophils with single round nuclei suggested that these cells were being produced in the lymph nodes themselves. Longcope believed that the eosinophils were attracted from the blood by positive chemotaxis but Pullinger considered that the available evidence supported the view that they were produced in the lymph nodes.

Polymorphonuclear leucocytes were absent in seventeen biopsies and present in the remaining fifty-three in varying numbers. They were usually less numerous than the eosinophils. In thirty-four biopsies plasma cells were seen in scanty to moderate numbers. They were frequently found in areas of fibrosis.

The identification of mitotic figures in the abnormal reticulum cells was uncommon although they could be found by searching in almost every biopsy.

Multinucleated cells with the histological features of a Langhan's giant cell have occasionally been found in sections of Hodgkin's gland (Reed, 1902; Longcope, 1903). Cells of this type were identified in two of our biopsies, one of which also showed the formation of a few sarcoid like structures similar to those described by Jackson and Parker (1947) and Smetana and Cohen (1956).

Only two biopsies (from the same patient) showed the co-existence of tuberculosis and Hodgkin's disease in the same gland (figs. 8, 9).

III. HODGKIN'S SARCOMA

It must be frankly admitted that the distinction between Hodgkin's disease and Hodgkin's sarcoma is one of degree only and

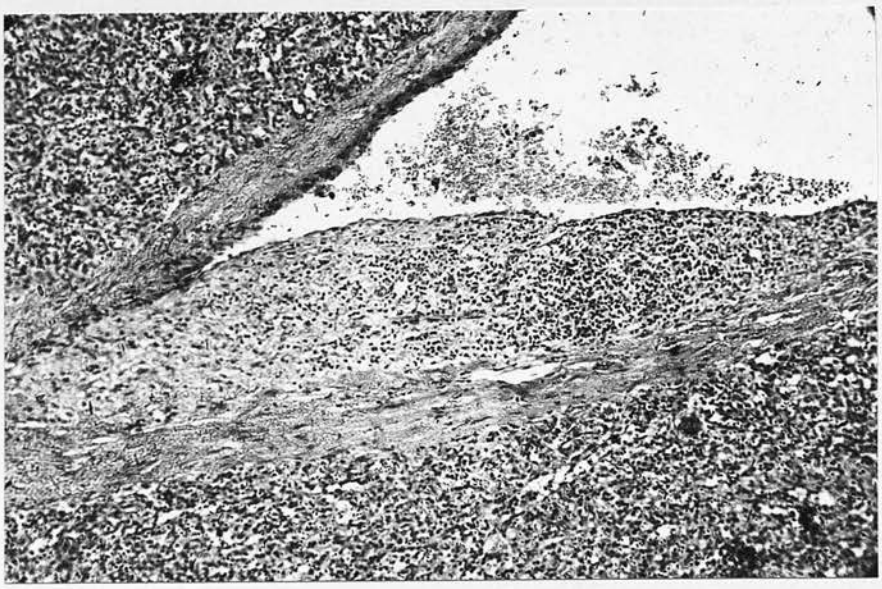

Fig. 10. Hodgkin's sarcoma (HS. 3). Spleen. Infiltration in wall of trabecular vein. (H. & E. X 55).

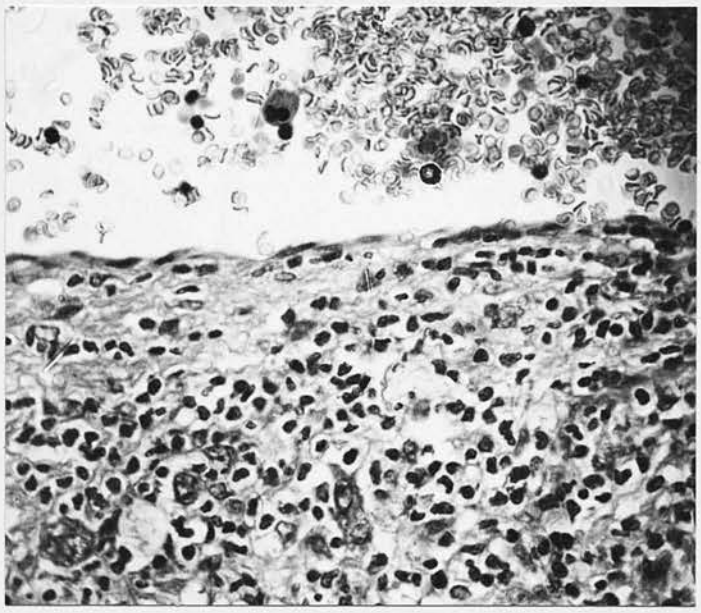

Fig. 11. Hodgkin's sarcoma (HS. 3). Spleen. Same as Fig. 10. Infiltration in wall of trabecular vein showing giant cells. (H. & E. X 330).

that it is not easy to state the criteria by which such a distinction can be made. There were eight biopsies (from eight patients) which it was considered could be classified as Hodgkin's sarcoma; seven were lymph nodes, the eighth a spleen.

The histological changes in Hodgkin's sarcoma were the same as those seen in Hodgkin's disease; the degree of activity was greater. The gland architecture was completely destroyed in all but one instance, invasion of the capsule more obvious, the multinucleated cells more frequent and more bizarre, mitotic figures and necrosis more frequent, fibrosis less common. In the one spleen examined the diagnosis of Hodgkin's sarcoma was based on the finding of invasion of the wall of a trabecular vein (figs. 10, 11) by tumour.

IV. INTERMEDIATE FORMS

In a number of instances difficulty was encountered in deciding whether to regard a biopsy as Hodgkin's disease or Hodgkin's sarcoma. The final decision was to classify all borderline cases as Hodgkin's disease. Eight appeared to border on reticular lymphoma and five on Hodgkin's sarcoma.

B. AUTOPSY

Autopsy material was available from eleven cases of Hodgkin's disease excluding case H. 7 which is discussed in chapter IX and from six cases of Hodgkin's sarcoma. The involvement (macroscopical and microscopical) of organs in these seventeen cases is shown in table XVI.

Table XVI

Involvement of Organs and other Findings at Autopsy

	Hodgkin's disease (11 autopsies)	Hodgkin's sarcoma (6 autopsies)
Peripheral lymph nodes	8	3
Mediastinal lymph nodes	9	3
Abdominal lymph nodes	9	5
Spleen	9	5 (a)
Liver	5	5
Lungs	4	3
Bone	1	2
Gastro-intestinal tract	-	3
Kidney	-	1
Heart	-	1
Adrenal	1	-
Pericardium	2	-
Pleura	2	-
Voluntary muscle	1	-
Skin	2	-
Testis	-	1
Ascites	3	-
Pleural effusion	3	-

(a) The 6th had previously been subjected to splenectomy.

The distribution of lesions at post mortem showed only a few features which merit comment. The spleen was found to be involved

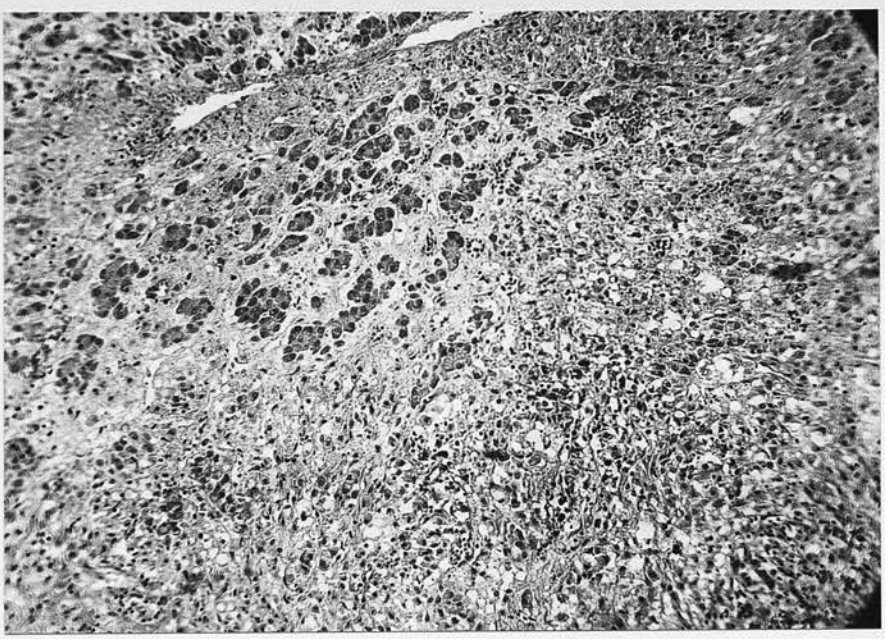

Fig. 12. Hodgkin's disease (H. 23). Suprarenal gland. Invasion by Hodgkin's disease. (H. & E. X 55). (Courtesy of Professor Payling Wright).

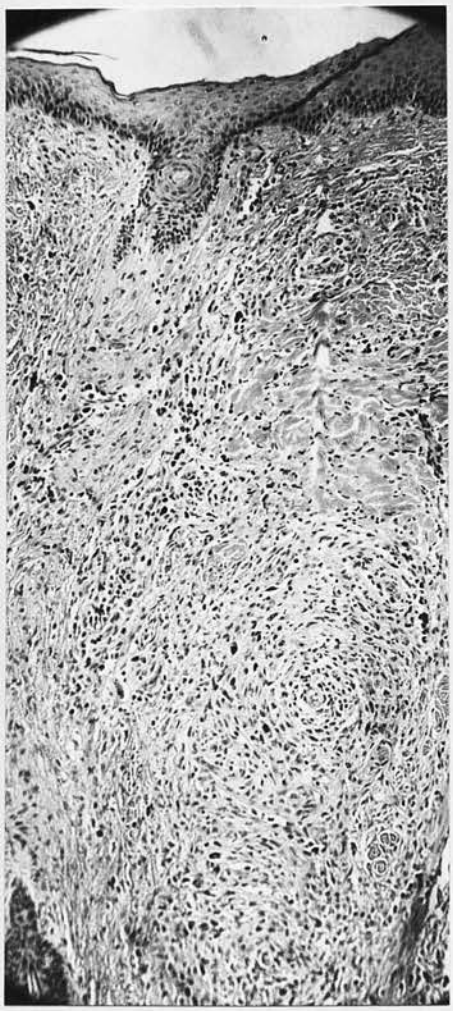

Fig. 13. Hodgkin's disease (H. 39). Skin. Infiltration of corium. (H. & E. X 55). (Courtesy Dr. H. de C. Baker).

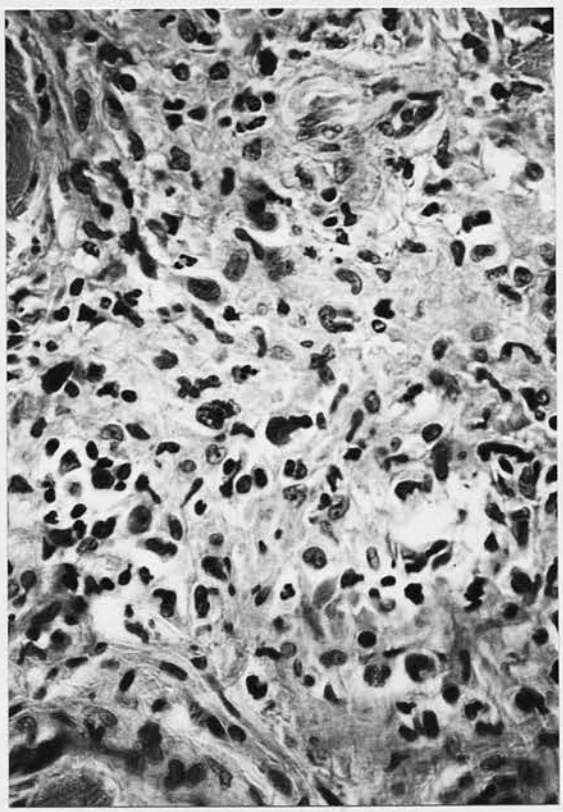

Fig. 14. Hodgkin's disease (H. 39). Skin. Same as Fig.13. (H. & E. X 330).

in all cases of Hodgkin's sarcoma in this series whereas Jackson and Parker (1947) found involvement of the spleen in less than one third of their autopsy material. The number of cases showing disease in bone is smaller than one would expect and is probably due to the difficulty of examining all bones.

The frequency with which the gastro-intestinal tract was involved is said to be higher in Hodgkin's sarcoma than in Hodgkin's disease (Jackson and Parker, 1947), although Wahl and Hill (1956) found gastric lesions in nine out of forty-three autopsies in Hodgkin's disease. In the present series gastro-intestinal involvement was seen in Hodgkin's sarcoma only.

As in Jackson and Parker's cases invasion of the adrenal gland in case H. 23 was from adjacent lymph nodes (fig. 12). The testis would appear to be a relatively unusual site for Hodgkin's sarcoma, being involved in two out of thirty-two cases in Jackson and Parker's series.

Extension of the disease process beyond the confines of an organ was seen naked eye in both diseases.

> In case H. 39 for example - a biopsy proven case of Hodgkin's disease - at autopsy a firm solid mass was found in the anterior mediastinum and this had infiltrated forwards through the intercostal muscles into the subcutaneous tissue and finally produced skin nodules (figs. 13, 14). The tumour also infiltrated the parietal pericardium and extended into the left lung.

Microscopical Appearances

Many of the patients who came to autopsy had been subjected to radiotherapy or treated with cyto-toxic drugs during their illness. Lumb (1954) considered that radiation produced fibrosis in lymphoid tumours but found no specific changes which could be attributed to chemotherapy.

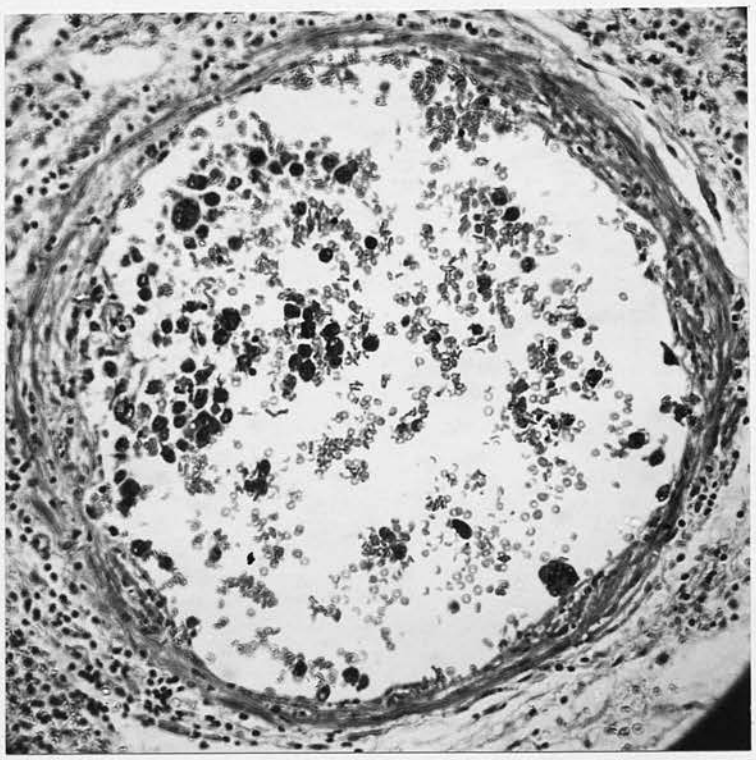

Fig. 15. Hodgkin's sarcoma (HS. 6). Tumour cells in a vessel in the peri-nodal connective tissue of an abdominal lymph node. (H. & E. X 110).

The differences between Hodgkin's disease and Hodgkin's sarcoma became even less obvious in autopsy material. When biopsy and autopsy material from Hodgkin's disease were compared there was an obvious tendency for the autopsy sections to show increased anaplasia with more bizarre cells and increase in mitotic activity, thus approaching the picture seen in Hodgkin's sarcoma. Necrosis and fibrosis were easily demonstrated in both diseases. The histological picture varied in glands from different parts of the body; from one area they might show a cellular picture, in others almost nothing but dense hyalinised collagen. Nuclear hyperchromatism, chromatolysis and karyorrhesis were frequently seen.

Erythrophagocytosis by histocytic cells in lymph nodes and by Kupffer cells in the liver was sometimes noted.

In one case of Hodgkin's sarcoma (H. 56) free tumour cells were seen in a blood vessel of a para-aortic gland (fig. 15). In life abnormal mononuclear cells had been present in the peripheral blood.

The hilar glands were the site of caseating tuberculosis in one case (H. 24) and this was the only evidence of tuberculosis in the autopsy material.

CHAPTER VII

FOLLICULAR LYMPHOMA

HISTORICAL

The disease now often referred to as follicular lymphoma (Gall and Mallory, 1942; Wetherley-Mein et al., 1952; Lumb, 1954, 1955) was first fully recognised by Brill, Baehr and Rosenthal in 1925 when they described three cases of 'Generalised giant lymph follicle hyperplasia of lymph nodes and spleen' for which they suggested the name 'splenomegalia lymphatica hyperplastica'. At first the condition was thought to be benign (Brill et al., 1925; Symmers, 1927) but later cases were reported in which there was a progressive change to lymphosarcoma (Baehr et al., 1931; Baehr, 1932; Gall et al., 1941), to Hodgkin's disease (Custer and Bernhard, 1948) and to "polymorphous cell sarcoma" (Symmers, 1938, 1942, 1948). Symmers also noted that follicular lymphoma might be associated with lymphatic leukaemia.

Other names which have been used to designate this condition include lymphoid follicular reticulosis (Robb-Smith, 1938), follicular lymphoblastoma (Baehr et al., 1931), giant follicle lymphoblastoma (Richter, 1948), giant follicle lymphoma (Jackson and Parker, 1947), giant follicular lymphoma (Harrison, 1956), macrofollicular lymphoma (Wright, 1956b) and Brill-Symmers disease.

THE CASES

There were six cases in which the histological diagnosis of follicular lymphoma was reasonably certain.

I. AGE AT FIRST ADMISSION

The ages of the six cases at first admission were 18 (two cases), 19, 25, 28 and 39. The fact that half of the cases were under the age of 20 is unusual but can probably be accounted for by the peculiar age structure of the population at risk. None of Jackson and Parker's (1947) thirty-nine cases were under 20 years of age and none of Wright's (1956) hundred and thirty-six cases under 25 years of age.

II. HISTORY ON ADMISSION

The symptoms complained of on first admission are detailed in table XVII.

Table XVII

Symptoms on First Admission

6 Cases of Follicular Lymphoma

Lump in neck	2
Lump in axilla	2
Lump in groin	3
Pain in chest	1
Haemoptysis	1
Lassitude	1

One case (FL. 1) was first detected when he was found to be anaemic on volunteering as a blood donor but on questioning gave a history of enlarged groin glands on one side for which he had consulted a medical officer four and a half years previously.

The length of history before first admission to hospital was under two months - two; five months - one; two years - one; several years - two.

III. CONDITION ON ADMISSION

The principal physical signs found are given in table XVIII.

Table XVIII

Physical Signs on Admission

6 Cases of Follicular Lymphoma

Enlarged lymph nodes restricted to one side of neck	2
Enlarged lymph nodes restricted to one groin	1
Two or more regions involved	3
Enlarged mediastinal shadow	-
Splenomegaly	1
Hepatomegaly	1

IV. COURSE OF DISEASE

In three cases no further extension of the disease took place. In the other three cases further enlargement of groups of glands noted on admission occurred.

In one case (FL. 1) abdominal masses, presumably enlarged glands, became obvious and X-ray evidence of mediastinal involvement appeared. This patient in the latter stages of the disease complained of severe pruritus and excoriated himself scratching. He died four years after first admission.

Splenomegaly and hepatomegaly developed in one case (FL. 6) and were accompanied by signs of hypersplenism for which splenectomy was eventually performed. The blood changes seen in this case are discussed later.

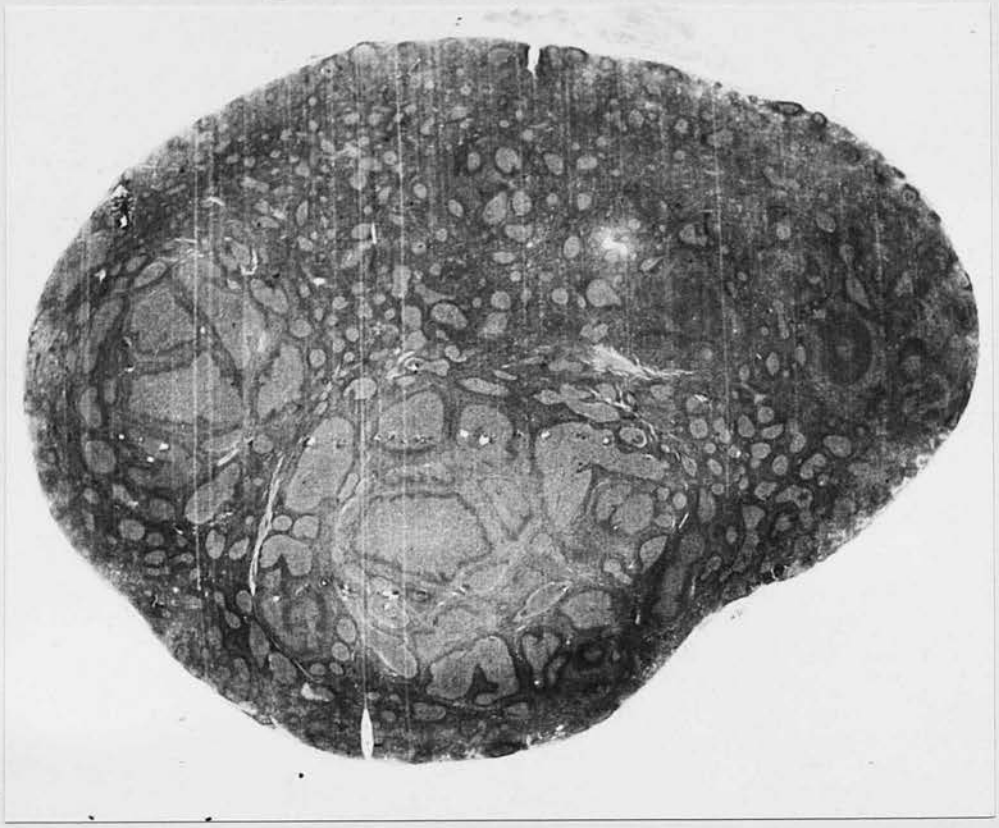

Fig. 16. Follicular lymphoma (FL. 2). Lymph node. Numerous follicles of varying size throughout the node. (H. & E. X 5.5).

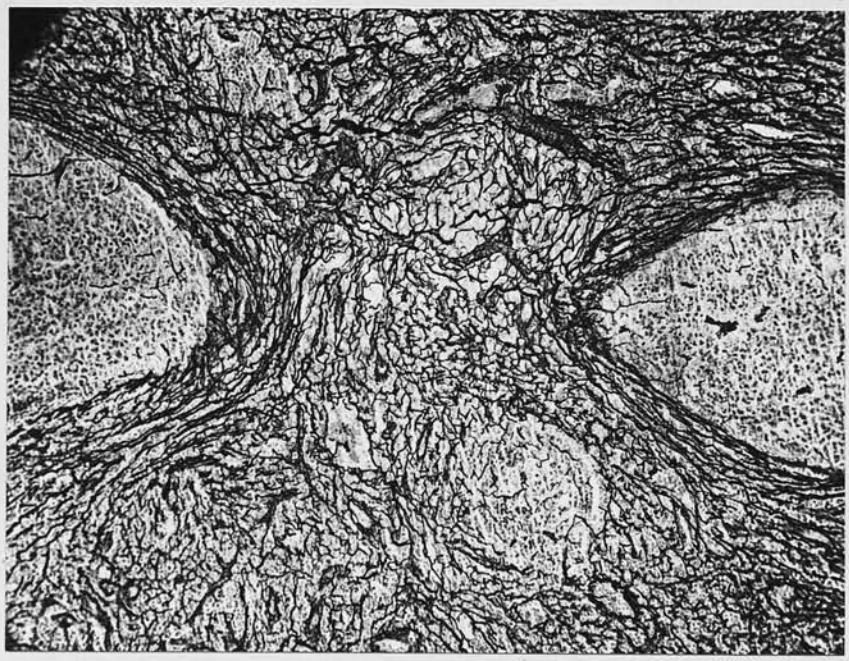

Fig. 17. Follicular lymphoma (FL. 2). Lymph node. Compression of reticulin around follicles. (Gordon and Sweets X 55).

Serous effusions often noted by other observers (e.g. Baehr and Rosenthal, 1927; Russel, 1951) were not a feature of our cases.

PATHOLOGY

A. BIOPSY

Eight lymph node biopsies and one spleen were available for study from the six cases.

Macroscopically it was sometimes possible to see an obvious follicular pattern on the cut surface of lymph nodes.

Microscopically the most obvious change in the lymph nodes was a numerical and dimensional increase in the follicles which were found throughout the whole node in all cases (fig. 16). The follicular pattern was well demonstrated in sections stained to show reticulin, the enlarged follicles being surrounded by compressed reticulin fibres (fig. 17). Reticulin was almost absent from the follicles themselves.

In one gland a number of lymphocytes were seen in the capsule but in the remaining seven the capsule was normal.

The centres of the follicles were composed of primitive reticular cells and large lymphocytes (lymphoblasts) in varying proportions while macrophage cells with phagocytosed particles were either absent or present only in small numbers. Mitotic activity was slight in five and moderate in three instances. The paler staining centre of each follicle was surrounded by a darker staining zone of small lymphocytes. Coalescence of follicles was noted in one biopsy.

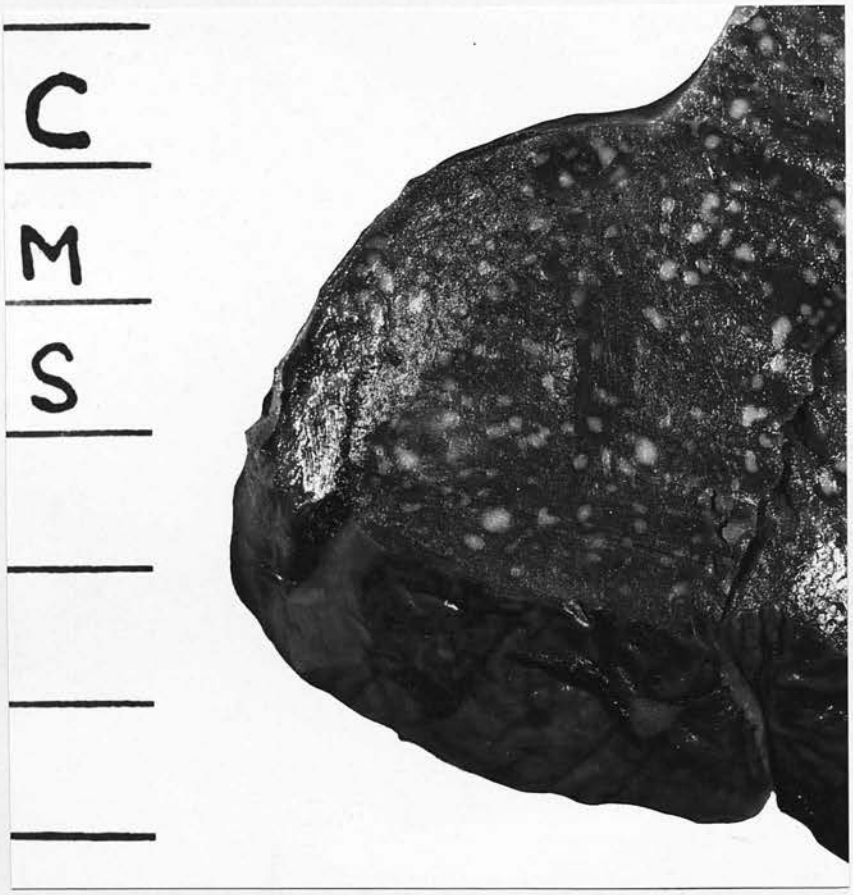

Fig. 18. Follicular lymphoma (FL. 6). Spleen. Numerous enlarged follicles.

The neoplastic follicles of follicular lymphoma can usually be distinguished from simple reactive follicles although sometimes such a distinction is difficult or even impossible to make. Both types of follicle were seen in the same gland in three biopsies.

The so-called 'cracking phenomenon' produced during fixation by the separation of follicles from the surrounding tissue was found in varying degrees in no less than six biopsies. This artefact has little diagnostic significance as it may be found in other conditions.

The spleen weighed 365 grams and the cut surface displayed numerous enlarged malpighian bodies (fig. 18). The histological changes in the spleen were confined to the white pulp where follicles similar to those described above were numerous.

B. AUTOPSY

In one case (FL. 1) a post mortem examination was performed. Histological examination showed that the disease had progressed to lymphosarcoma. Details of the post mortem findings have for convenience been included with the other lymphosarcomas.

CHAPTER VIII

LYMPHOSARCOMA, RETICULUM CELL SARCOMA AND MIXED CELL SARCOMA

HISTORICAL

The separation of lymphosarcoma from Hodgkin's disease by Kundrat (1893) and the identification of reticulum cell sarcoma by Roulet (1930, 1932) has already been described. Ever since Roulet's papers were published there has been a lack of uniformity in the manner in which different authors have applied the terms lymphosarcoma and reticulum cell sarcoma to these two tumours which are closely related histogenetically.

Sugarbaker and Craver (1940) used the term lymphosarcoma to include reticulum cell lymphosarcoma, giant follicular lymphoma and malignant lymphocytoma. They studied one hundred and ninety-six cases of which one hundred and eighty-four were classified as reticulum cell lymphosarcoma. Stout (1942) divided one hundred and sixty-four lymphosarcomas into lymphocyte cell type (fifty-five), reticulum cell type (eighty-nine) and giant follicle type (twenty). Recently Evans (1956) has followed a similar practice by dividing the lymphosarcomas into lymphocytic lymphosarcoma, lymphoblastic lymphosarcoma and reticulum cell sarcoma.

On the other hand Robb-Smith (1938) classified all sarcomata as reticulosarcoma of which he recognised ten subtypes including lymphoblastic sarcoma and lymphosarcoma.

Warren and Picena (1941) separated the sarcomas of lymphoid tissue into reticulum cell type, mixed type (combination of reticulum

cell and lymphoid cell), lymphoblastic type and lymphocytic type. Of their cases only 3.6% were reticulum cell type - a proportion very different from that given by Sugarbaker and Craver and by Stout. Gall and Mallory (1942) distinguished stem cell and clasmatocytic varieties of reticulum cell sarcoma and lymphoblastic and lymphocytic lymphoma.

The names lymphosarcoma and reticulum cell sarcoma were used synonymously by Harvey et al. (1940).

A number of workers regard reticulum cell sarcoma as a less differentiated tumour than lymphosarcoma (Warren and Picena, 1941; Evans, 1956), but Lumb (1954) considers that reticulum cell sarcoma and lymphosarcoma represent two different lines of differentiation from the primitive mesenchymal cell. Whichever view is correct there is no doubt that intermediate forms may be found with varying proportions of reticulum cells and lymphocytes.

THE CASES

There were eleven cases of lymphosarcoma, eight cases of reticulum cell sarcoma and two cases which have been classified as mixed cell sarcoma. Reticulum cell sarcoma of bone has not been included.

I. AGE AT FIRST ADMISSION

This is shown for all cases except one in table V. The one remaining patient was a Chelsea pensioner aged 72.

II. HISTORY ON ADMISSION

The symptoms complained of on first admission are detailed in table XIX.

Table XIX

Symptoms on First Admission - 21 Cases of Sarcoma

	Lympho-sarcoma	Reticulum cell sarcoma	Mixed cell sarcoma
Lump in neck	3	3	-
Lump in axilla	-	1	-
Abdominal pain or discomfort	4	3	2
Vomiting	1	-	1
Haematemesis	-	-	1
Dyspnoea	-	1	-
Cough	1	-	-
Loss of weight	2	1	-
Fever	1	3	-
Pain limbs, back or neck	5	3	2
Sore throat	2	1	-
Swelling knee	1	-	-
Swelling ankle	-	1	-

One case was first detected at a routine medical examination prior to release.

The length of history before first admission to hospital is given in table XX.

Table XX

Length of History Before Admission - 21 Cases of Sarcoma

	Lympho-sarcoma	Reticulum cell sarcoma	Mixed cell sarcoma
Under 1 week	-	2	-
1 - 2 weeks	4	1	1
2 - 4 weeks	2	1	-
1 - 2 months	2	-	1
2 - 4 months	1	2	-
8 - 9 months	1	-	-
4 years	1	-	-
Not readily determined	-	2	-

III. CONDITION ON ADMISSION

The principal signs noted on admission are summarized in table XXI.

Table XXI

Condition on Admission - 21 Cases of Sarcoma

	Lympho-sarcoma	Reticulum cell sarcoma	Mixed cell sarcoma
Number of cases	11	8	2
Enlarged lymph nodes restricted to one side of neck	1	1	-
Enlarged lymph nodes in two or more regions	5	5	-
Enlarged mediastinal shadow (X-ray)	2	2	-
Ulceration of tonsils	1	-	-
Signs of acute abdomen	1	-	-
Splenomegaly	2	-	-
Hepatomegaly	-	1	-
Abdominal mass	2	2	1
Ascites	-	1	-
Oedema one or both legs	1	1	-
Pyrexia	2	2	-
Swollen and tender ankles	-	1	-

IV. COURSE OF THE DISEASE

Generally these cases ran a rapidly progressive course during which many new manifestations of the disease process were noted (table XXII).

Table XXII

Course of Disease - 21 Cases of Sarcoma

	Lympho-sarcoma	Reticulum cell sarcoma	Mixed cell sarcoma
Number of cases	11	8	2
Enlargement of further groups of superficial nodes	2	5	-
Development of enlarged mediastinal shadow	2	-	-
Development of abdominal mass	2	1	-
Splenomegaly	4	3	-
Hepatomegaly	3	4	-
Involvement of (a) nerve	2	1	-
(b) lung	-	1	-
(c) skin	-	1	-
Involvement of bone	-	3	-
Development of mass in nasopharynx	1	1	-
Gross enlargement tonsil	2	-	-
Vomiting	4	-	-
Jaundice	-	1	-
Haematemesis	1	-	1
Melaena	1	-	-
Epistaxis	2	-	-
Purpura	2	-	-
Pyrexia	2	2	-
Papilloedema	1	-	-
Pleural effusion	3	-	-
Oedema legs	2	-	-

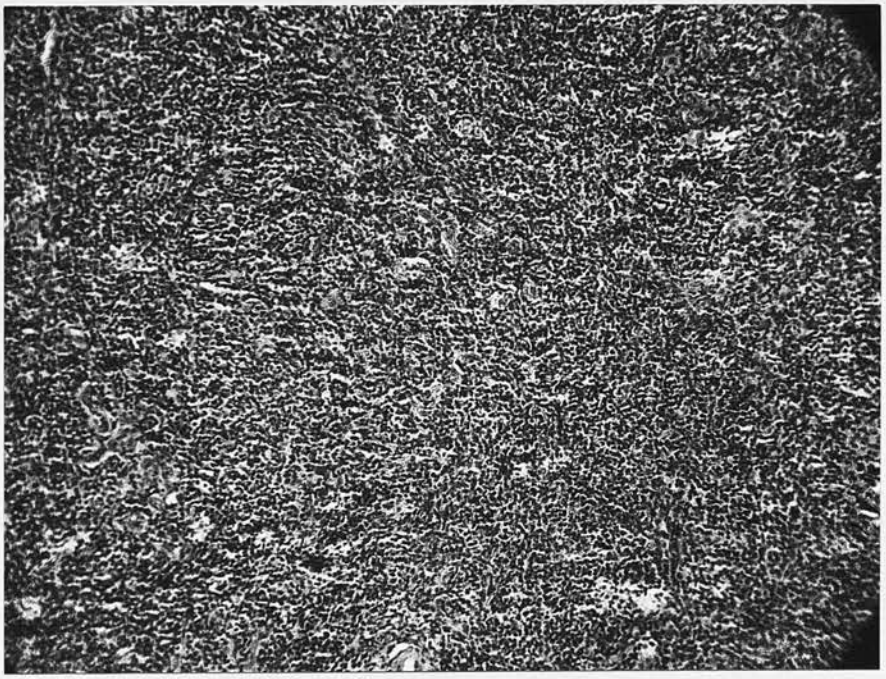

Fig. 19. Lymphosarcoma (LS. E 4). Lymph node. Sheet of small lymphocytes. (H. & E. X 55).

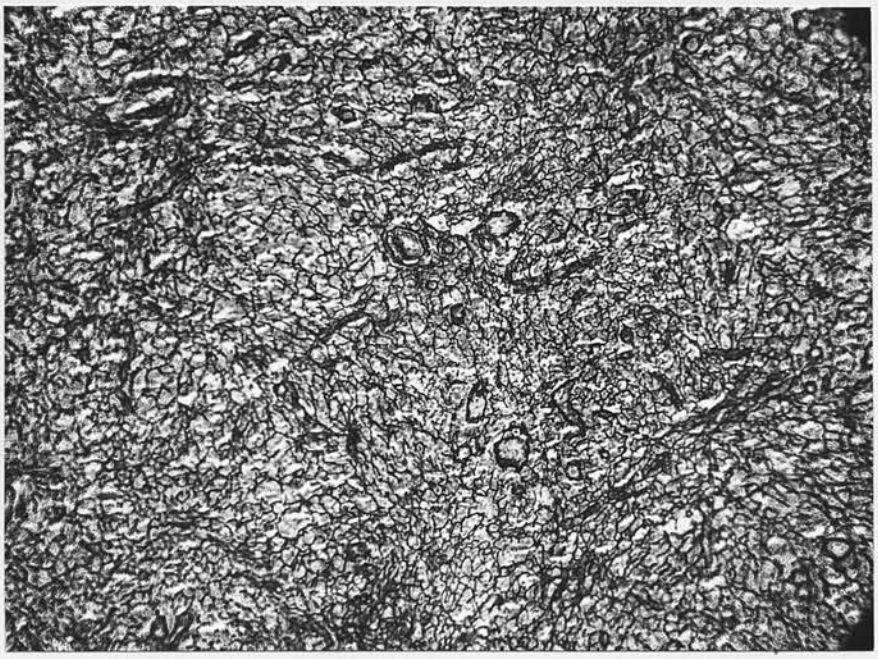

Fig. 20. Lymphosarcoma (LS. E 4). Lymph node. Same gland as Fig. 18. Unusual abundance of reticulin fibres, many related to blood vessels. (Gordon and Sweets X 55).

It is interesting to note the high proportion of signs and symptoms referable to the gastro-intestinal tract.

There was clinical evidence of tumour in the nasopharynx or tonsils in three out of the twenty-one cases. Reticular tissue is widespread in the nasopharynx and its involvement in lymphoid tumours is therefore to be expected (Harman et al., 1956).

PATHOLOGY

A. BIOPSY

Six positive biopsies were obtained from five patients out of the eleven cases of lymphosarcoma. Positive biopsies were obtained from all the cases of reticulum cell sarcoma and from one of the two cases of mixed cell sarcoma. The sites from which these positive biopsies were obtained are given in table XXIII.

Table XXIII

Biopsy Sites - 21 Cases of Sarcoma

	Lympho-sarcoma	Reticulum cell sarcoma	Mixed cell sarcoma
Cervical node	3	4	-
Axillary node	-	2	-
Inguinal node	2	-	-
Node site not stated	-	1	-
Caecal region	1	-	1
Small intestine	-	1	-

In the remainder of cases the diagnosis was established at autopsy.

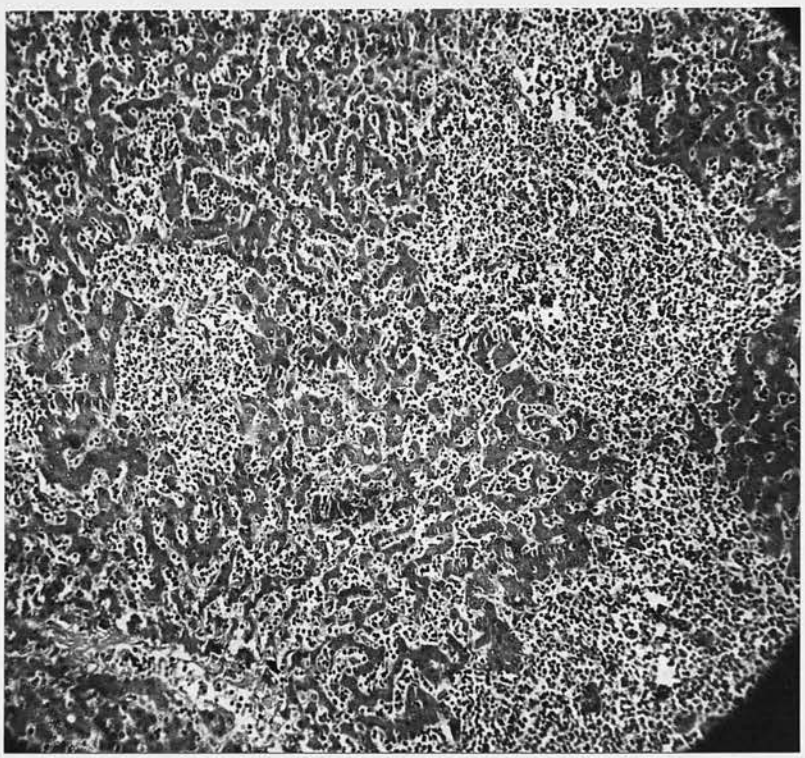

Fig. 21. Lymphosarcoma (LS. 5). Liver.
Diffuse and focal infiltration.
(H. & E. X 55).

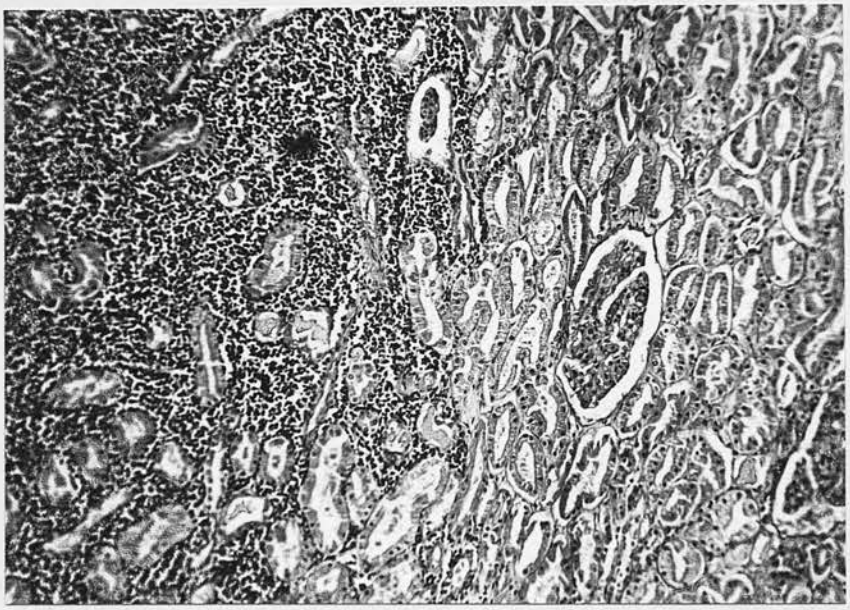

Fig. 22. Lymphosarcoma (LS. 5). Kidney.
Clear distinction between area of infiltration (left) and uninvolved kidney (right).
(H. & E. X 55).

I. LYMPHOSARCOMA

The lymph nodes were enlarged up to 4.5 cms., firm and usually presented a uniform yellowish-white cut surface.

The architecture of the lymph nodes was partially or completely destroyed and replaced by sheets of lymphocytes. These varied from small to large lymphocytes in different cases, although they were usually of uniform size in any one biopsy. Mitotic activity was moderate to marked.

In two biopsies from one patient (LS. 8) a definite follicular pattern could be seen throughout the gland, the follicles resembling in many respects the follicles of follicular lymphoma, but differing in being less sharply defined. Other features of lymphosarcoma e.g. capsular invasion and extension to peri-glandular fat, were present. In the sections from a further two cases (LS. 2 and 3) there was also an impression, although less definite, that the lymphosarcoma had a follicular pattern and this impression was strengthened by a study of reticulin stained sections.

In several biopsies it was possible to identify a number of abnormal reticulum cells scattered throughout the lymphocytes and eosinophils were occasionally found. In one section a sarcoid like follicle was present.

Reticulin was normally not increased in lymphosarcoma but in one instance was moderately abundant in relation to numerous blood vessels in the gland. This rather unexpected finding has since been seen in another case not included in the main series (LS. E4, see figs. 19, 20).

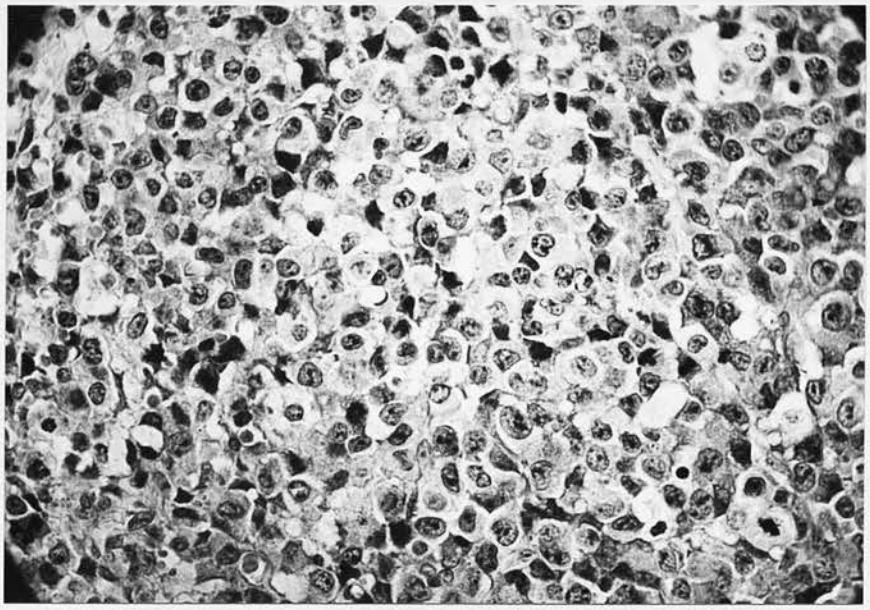

Fig. 23. Reticulum cell sarcoma (RCS. 2). Lymph node. Sheet of reticulum cells tending to form a syncytium. (H. & E. X 330). (Courtesy Dr. W. Whitelaw).

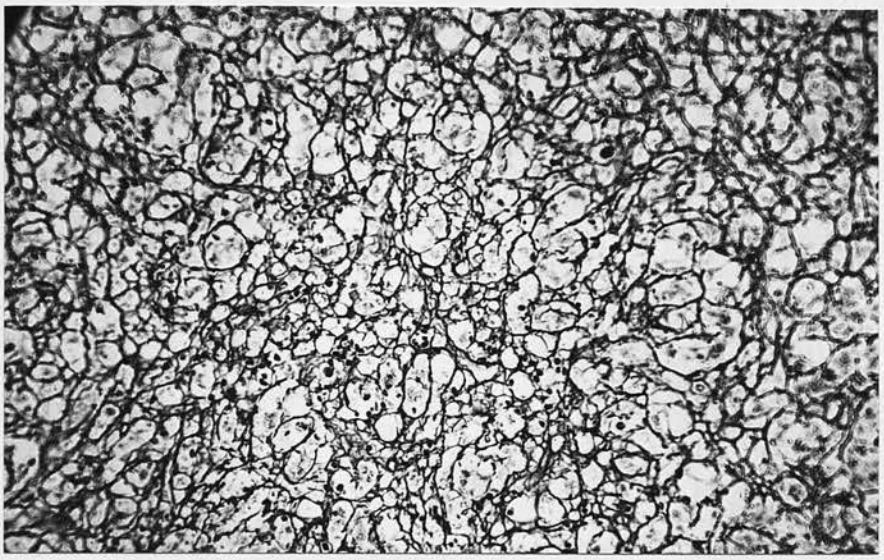

Fig. 24. Reticulum cell sarcoma (RCS. 2). Lymph node. Same node as Fig. 23. Reticulin fibres intimately connected with tumour cells. (Gordon and Sweets X 110).

II. RETICULUM CELL SARCOMA

Naked eye the glands showed no characteristic features which could be used to distinguish them from the glands in other lymphoid tumours.

Destruction of the lymph node architecture was usually complete, the lymphoid tissue being replaced by masses of abnormal reticulum cells often similar to those seen in Hodgkin's disease (fig. 23). In several tumours the cell boundaries merged to form a distinct syncytium. Multinucleated reticulum cells were present in half of the biopsies. Lymphocytes in varying numbers and rarely eosinophils were found among the reticulum cells. Invasion of and penetration beyond the capsule were frequent. Reticulin was usually but not always increased (fig. 24). Mitotic activity was obvious in most.

Unfortunately no report on the naked eye appearance of the tumour of jejunum can be traced. Histological sections showed ulceration of the mucosa and infiltration of all coats of the wall by abnormal reticulum cells. Numbers of lymphocytes, plasma cells and eosinophils were also present the eosinophils being very numerous around the spreading edge of the tumour. There was tendency for the tumour cells to have a trabecular arrangement.

III. MIXED CELL SARCOMA

This term has been used to describe those tumours in which lymphocytes and abnormal reticulum cells were present in approximately equal numbers, thus making the distinction between lymphosarcoma and reticulum cell sarcoma impossible. These intermediate forms presented no special features.

B. AUTOPSY

Autopsies were performed on six cases of lymphosarcoma, two cases of reticulum cell sarcoma and one of mixed cell sarcoma. In addition details of the one fatal case of follicular lymphoma (FL. 1) have been included in this section as the histological picture found at post mortem was that of typical lymphosarcoma.

The macroscopical findings are listed in table XXIV.

Table XXIV

Involvement of Organs and other Findings at Autopsy in 10 Cases of Sarcoma

	Lympho-sarcoma (7 autopsies)	Reticulum cell sarcoma (2 autopsies)	Mixed cell sarcoma (1 autopsy)
Superficial lymph nodes	5	1	-
Mediastinal lymph nodes	4	1	-
Abdominal lymph nodes	6	2	1
Spleen	2	-	-
Liver	3	-	-
Stomach	2	-	1
Small intestine	1	-	-
Kidneys	4	-	-
Bone	2	1	-
Heart	1	-	-
Diaphragm	1	-	-
Dura	1	-	-
C.N.S. (cord)	-	1	-
Pleural effusion	2	1	-
Ascites	-	1	-
Jaundice	-	1	-

I. LYMPH NODES

Sections showed the same histological changes as the biopsy material already described.

II. SPLEEN

Two of the three enlarged spleens from cases of lymphosarcoma showed no distinguishing naked eye features but microscopically there was diffuse infiltration by lymphocytes. In the third enlargement was due only to infarct.

In reticulum cell sarcoma no definite histological evidence was found of disease in the two spleens examined although in one suspicious looking cells were present in small numbers.

III. LIVER

In only one case of lymphosarcoma were naked eye nodules (up to 7 mm. in diameter) found throughout the liver. Microscopically in this case and in two others showing no obvious naked eye involvement there was diffuse infiltration throughout the liver with marked involvement of the portal tracts (fig. 21).

Of the two livers from cases of reticulum cell sarcoma, one was enlarged, the other normal in size, and neither showed any conclusive evidence of infiltration microscopically.

IV. GASTRO-INTESTINAL TRACT

In three instances post mortem examination revealed tumour in the stomach. One stomach was involved by extension from lymphosarcomatous glands on its posterior aspect; in the second (lymphosarcoma) a large malignant ulcer ($3\frac{1}{2}$" diameter) on the lesser curvature had eroded a blood vessel; in the third (mixed cell sarcoma) three malignant ulcers, including one $3\frac{1}{2}$" in diameter, were found.

The lymphosarcoma of the small intestine was predominantly infiltrative in type, the mucous membrane being intact except in one area where ulceration had occurred. The appendix was also involved in this case.

V. KIDNEYS

In all four instances in which the kidneys were involved by lymphosarcoma, obvious naked eye deposits (up to several cms. in diameter) were visible. Microscopically the renal involvement was focal with intervening areas of normal tissue (fig. 22) thus differing from the picture seen in lymphatic leukaemia.

VI. OTHER ORGANS

In addition to the organs listed in table XXIV evidence of involvement of lungs (two), supra-renal (one) and pituitary (one) was found in the material from the lymphosarcoma cases.

C. COMMENTS

I. TRANSITIONS IN HISTOLOGY

No trace of a follicular pattern was detectable in the autopsy sections from case FL. 1, whereas the biopsy specimen taken four years before death showed typical follicular lymphoma. The post mortem histology was that of lymphosarcoma. This was the only case in which transition from follicular lymphoma to lymphosarcoma was proved but the finding of a follicular pattern in the biopsies of three cases of lymphosarcoma suggests that these cases may also have begun as follicular lymphomas.

II. INVOLVEMENT OF THE GASTRO-INTESTINAL TRACT

In no less than seven cases out of a total of twenty-one were lesions found in the stomach and intestine (table XXV).

Table XXV

Involvement of Gastro-Intestinal Tract

No.	Site	Operation	Autopsy
LS. 4	Stomach	Laparotomy	Local spread only.
LS. 6	Stomach	Nil.	Generalised disease with secondary invasion of stomach.
MS. 2	Stomach	Nil.	Spread to regional glands.
LS. 7	Small intestine	Laparotomy	Extensive local spread and pleural nodules.
RCS.6	Small intestine	Resection	Nil.
LS. 1	Caecum	Ileo-transverse colostomy	Nil.
MS. 1	Caecum	Ileo-transverse colostomy	Nil.

In six of the seven cases the operation or autopsy findings suggested that the tumours began as primary lesions in the gastro-intestinal tract. In the remaining case (LS. 6) the disease was generalised and the stomach was involved by invasion from surrounding tumour. The occurrence of primary intestinal lymphosarcoma and reticulum-cell sarcoma has recently received renewed attention (Skrimshire, 1955; Irvine and Johnson, 1955; Thorbjarnarson et al., 1956).

III. SPREAD OF TUMOURS

Lymphosarcoma and reticulum-cell sarcoma may arise as a primary tumour in one site or organ or may be generalised from the beginning (Robb-Smith, 1939, 1956b; Marshall 1956a). In the

present series examples of multi-focal origin were seen in the cases presenting with generalised lymphadenopathy and of unifocal origin in the primary gastro-intestinal tumours.

Case LS. 5 illustrates well the widespread dissemination which may be found in lymphosarcoma. At autopsy lymphatic glands, liver, spleen, kidneys, suprarenals, bone, heart, dura and pituitary were all involved.

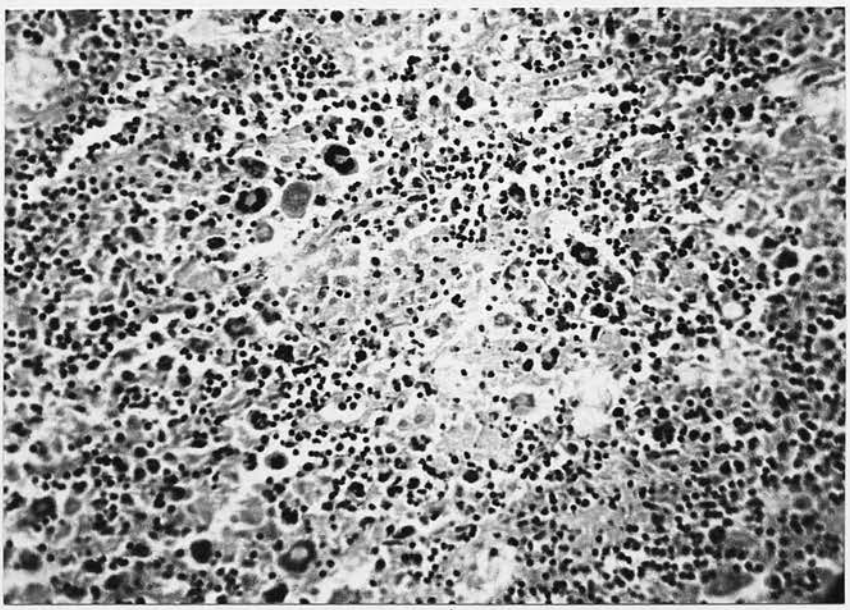

Fig. 25. Case Misc. 1. Lymph node. Pleomorphic proliferation with unusual giant cells. (H. & E. X 110).

CHAPTER IX

MISCELLANEOUS CASES

In this group have been placed :-

A. a case impossible to classify (Misc. 1).

B. two cases (Misc. 2 and 3) showing the typical clinical and histological features of 'histiocytic medullary reticulosis'. Among the cases classified as Hodgkin's disease was one (H. 7) which eventually developed into histiocytic medullary reticulosis. For convenience all three are discussed together.

A. AN UNCLASSIFIED CASE

An officer's wife, age 57, presented with a history of a lump in the right side of her neck for 5 weeks. One large tender diffuse mass was felt behind the angle of the right mandible and this extended half way down the sterno-mastoid. There were no other glands, no abnormality was detected in the abdomen and chest X-ray was normal.

A biopsy was performed and the specimen received in the laboratory consisted of a lymph node 4 x 2 x 1.5 cms. with a uniform pale yellow cut surface. Histologically (fig. 25) the picture was quite unusual. The architecture was completely destroyed and replaced by sheets of loosely arranged cells which included large multinucleated eosinophilic cells with hyperchromatic nuclei arranged in horse shoe fashion, in rosettes or irregularly, together with smaller eosinophilic cells with small round vesicular nuclei, polymorphs, lymphocytes and a few fibroblasts. There was a considerable reticulin network.

The giant cells resembled those in the illustration of Israëls's (1953) case No. 8 which he called "giant cell reticulosis". However "giant cell reticulosis" was regarded by Israëls as a synonym for "histiocytic medullary reticulosis" and there was no other evidence that our case belonged to this category.

The patient was treated with radiotherapy, but extension occurred, mainly in the abdomen and the death occurred nine months after first admission to hospital. There was no post mortem.

B. HISTIOCYTIC MEDULLARY RETICULOSIS

I. INTRODUCTION

In 1939 Bodley-Scott and Robb-Smith described ten cases comprising four of their own and six from the literature of a rapidly fatal disease characterised by fever, generalised lymphadenopathy, splenomegaly and hepatomegaly. Anaemia, leucopenia, purpura and jaundice were common in these patients. The principal pathological finding was a proliferation in the reticular tissue of histiocytic cells with much erythrophagocytosis.

Few further cases were reported until Marshall (1956b) published an account of eight cases with a full description of the pathological findings.

II. THE CASES

(a) Clinical

The first case (Misc. 2) was an officer, age 23, who reported sick on account of an ulcer of the palate. Biopsy from the palate and from an enlarged cervical gland showed only chronic inflammation.

The second case (Misc. 3) was a soldier, age 24, who was admitted to hospital complaining of gastro-intestinal upset and swelling of the abdomen. No biopsy was performed.

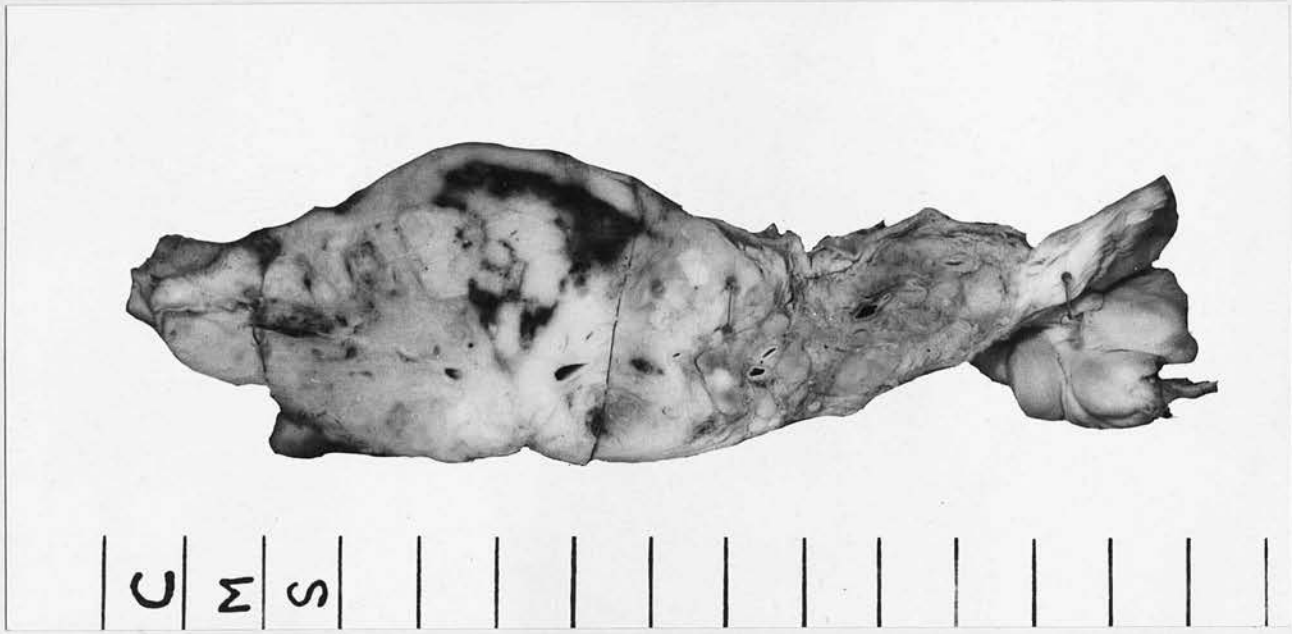

Fig. 26. Histiocytic medullary reticulosis (Misc. 3).
Mesenteric lymph nodes. Areas of haemorrhage are clearly visible.

The third case (H. 7), a fit soldier of 18, was found in October 1949 on mass miniature radiography to have an enlarged mediastinal shadow. A palpable gland was discovered in the right side of the neck and this was excised. The histology showed Hodgkin's disease (figs. 27, 28). The patient was given radiotherapy to the mediastinum with very good response, the chest X-ray after treatment being normal. In February 1950 he was invalided from the army. He remained fit until May 1951 when he developed jaundice. He was then admitted to Westminster hospital ? infective hepatitis.

The further progress (table XXVI) of all three cases was very similar and conformed to the published descriptions of the clinical course of histiocytic medullary reticulosis. All three died.

Table XXVI

Clinical Features in Three Cases of Histiocytic Medullary Reticulosis

	Misc. 2	Misc. 3	H. 7
Pyrexia	+	no record	+
Jaundice	+	+	+
Splenomegaly	+	+	+
Hepatomegaly	+	+	+
Lymphadenopathy	+	-	-
Anaemia	+	+	+
Leucopenia	+	+	+
Duration	5 months	2 months	6 months ≠

≠ From admission in May 1951 with jaundice

The third case (H. 7) developed thrombocytopenia before death.

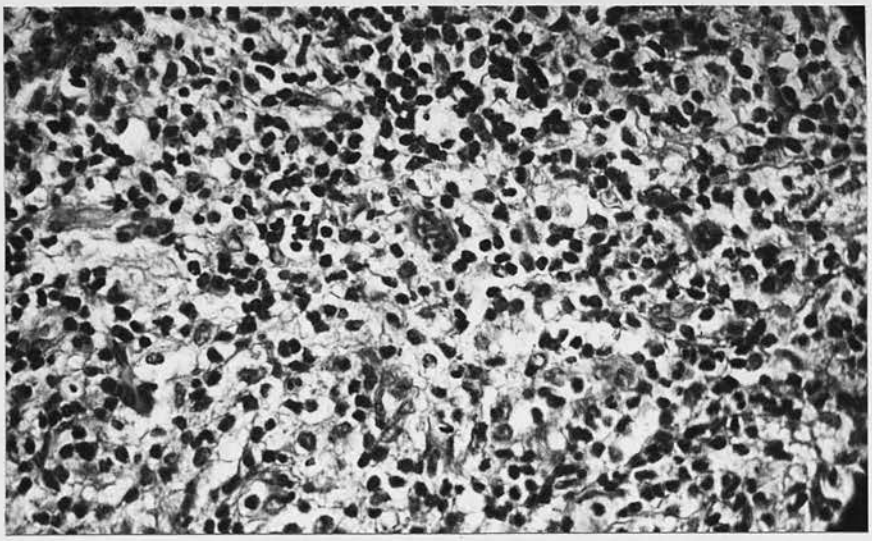

Fig. 27. Case H. 7. Lymph node. Biopsy.
Histological features of Hodgkin's disease.
Binucleated giant cell in centre of field.
(H. & E. X 330).

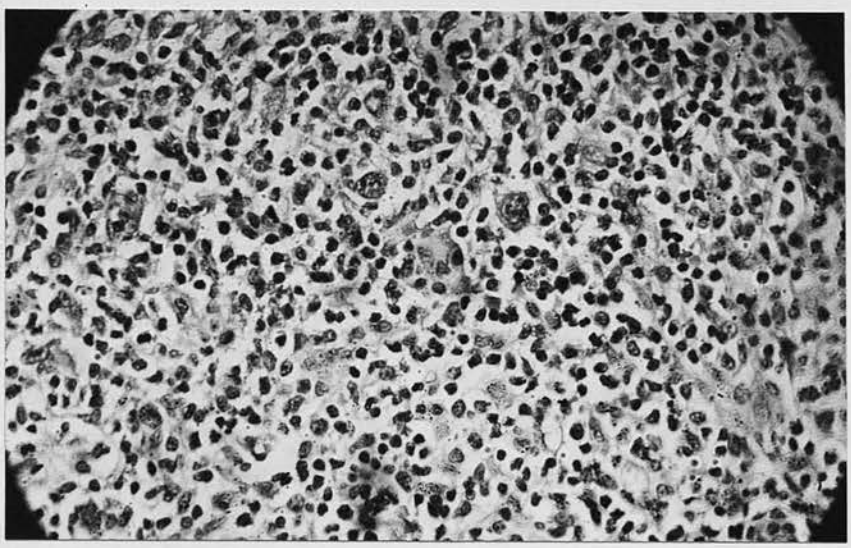

Fig. 28. Case H. 7. Lymph node. Biopsy.
Same slide Fig. 27. Pleomorphic picture
of Hodgkin's disease. (H. & E. X 270).

(b) Autopsy

The autopsy findings listed below (table XXVII) are similar to those described by Marshall.

Table XXVII

Principal Autopsy Findings in Three Cases of Histiocytic Medullary Reticulosis

	Misc. 2	Misc. 3	H. 7 [*]
Ascites	+	+	+
Pleural effusion	-	+	-
Spleen	Enlarged	840 g.	1900 g.
Liver	2030 g.	2185 g.	4500 g.
Abdominal lymphadenopathy	+	+	+

In all three the lymphadenopathy was most marked in the abdominal glands. In Misc. 2 the glands were mainly in relation to the head of the pancreas and around the bile duct, although there were also a number of smaller glands (up to 1 cm.) in the mesentery. In Misc. 3 the matted mass of glands (8 x 5 x 4 cms.) was present in the root of the mesentery and these glands were soft with areas of haemorrhage (fig. 26). Further glands were found along the aorta. The enlarged glands in H. 7 were most obvious in the porta hepatis.

The liver in Misc. 2 was enlarged but otherwise normal to the naked eye. In Misc. 3 the liver was widely infiltrated by nodules of soft whitish-growth up to 2 cms. diameter in which haemorrhage was common. The liver in H. 7 was involved by direct extension from

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[*] Material and post-mortem notes placed at my disposal by Dr. G. Lumb.

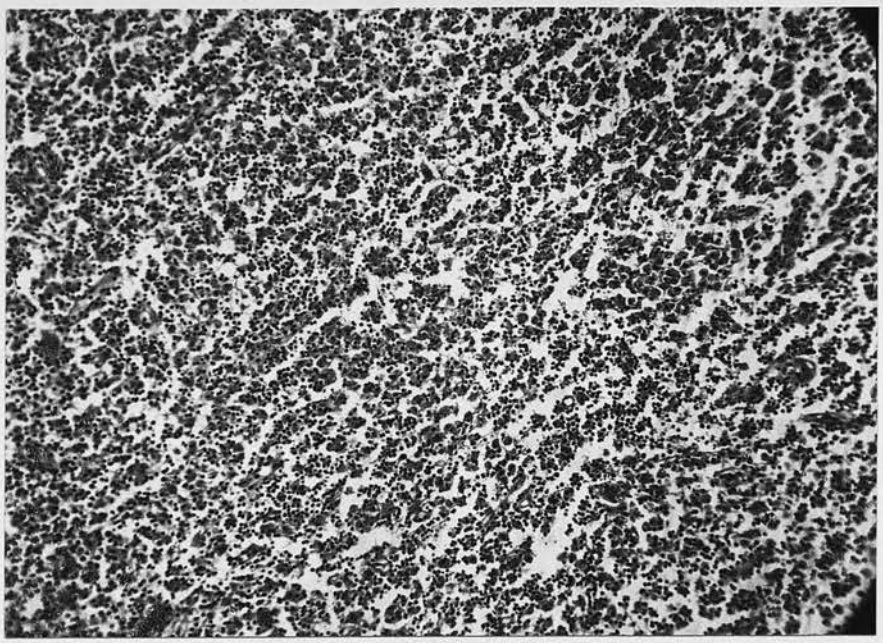

Fig. 29. Case H. 7. Lymph node. Autopsy. Diffuse proliferation of lymphocytes and histiocytes. (H. & E. X55).

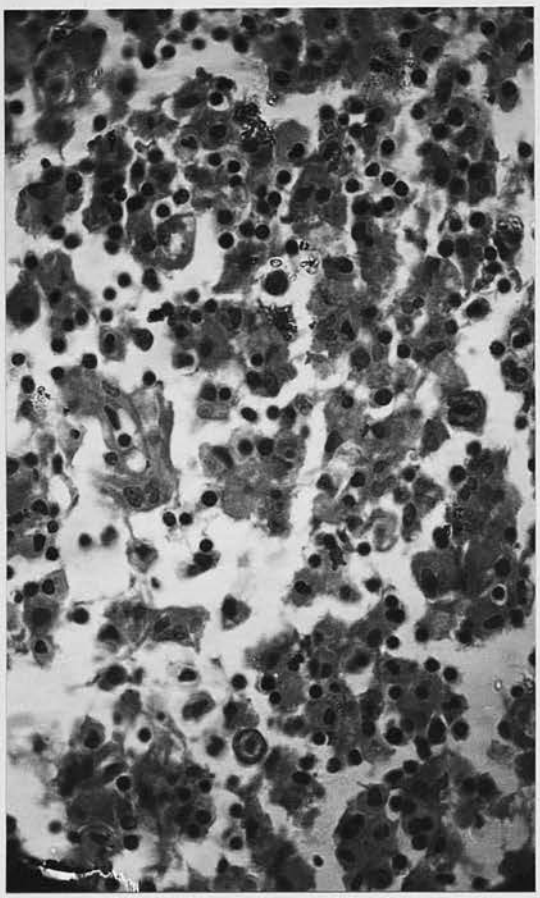

Fig. 30. Case H. 7. Lymph node. Autopsy. Lymphocytes and histiocytes, some of which show erythrophagocytosis. (H. & E. X 330).

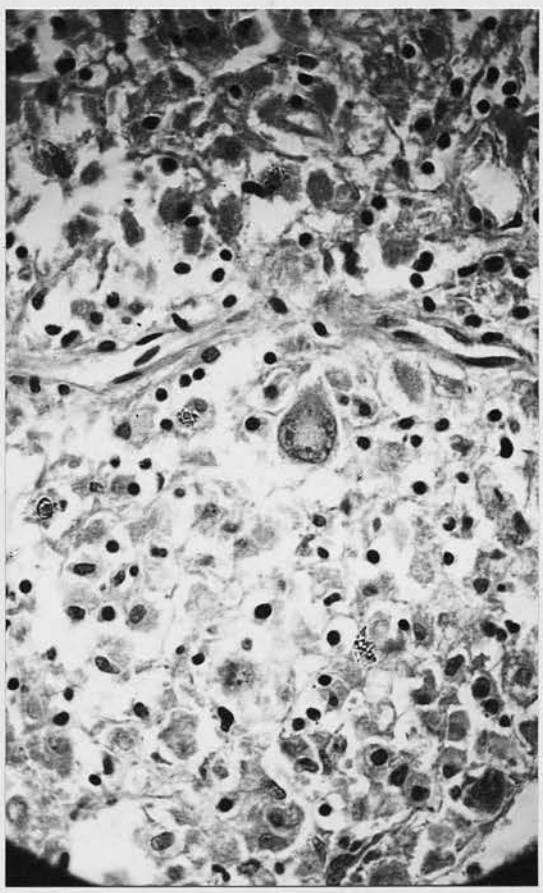

Fig. 31. Case H. 7. Lymph node. Autopsy. Multinucleated cell, histiocytes and lymphocytes. (H. & E. X 330).

the glands in the porta hepatis but in addition numerous whitish flecked areas were seen scattered throughout its substance.

All three spleenswere enlarged. The spleen in Misc. 3 showed evidence of perisplenitis. The cut surface was dark red in colour with a number of paler areas of infarct 0.8 to 2 cms. in width. In H. 7 the spleen was firm with a fleshy external appearance. Numerous greyish flecks were detected throughout its substance.

The bone marrow in H. 7 was noted to be of a purplish fleshy appearance.

The remaining organs showed no evidence of involvement except for the finding of several firm round yellowish nodules about 1 cm. in diameter in the lungs of Misc. 2.

(c) Histology

The principal histological changes observed in the three cases were similar, differing only in extent and in the relative frequency of the component features.

Most of the affected lymph nodes showed complete destruction of the normal architecture and its replacement by a proliferation of cells of various types (figs. 29 - 31). Histiocytes of normal appearance many showing marked erythrophagocytosis and phagocytosis of nuclear material were constant and prominent in the lesions. In addition to the histiocytes of normal appearance there were atypical eosinophilic cells which were not phagocytic. Giant forms of these cells often possessed convoluted nuclei sometimes arranged in rosette formation. Lymphocytes and reticulum cells were also identified in the cellular proliferations. Mitotic activity was

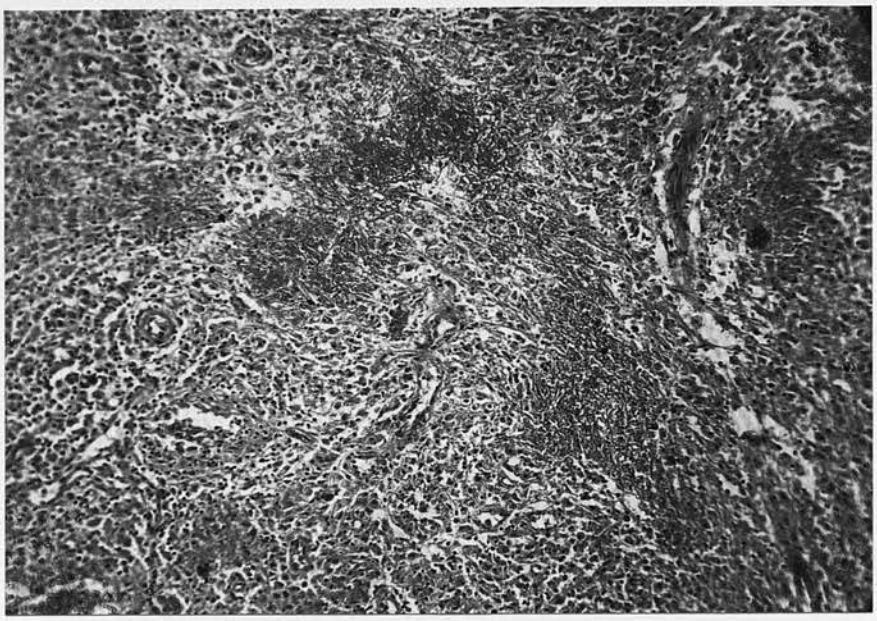

Fig. 32. Case H. 7. Lymph node. Autopsy.
Areas of fibrinoid necrosis. (H. & E. X 55).

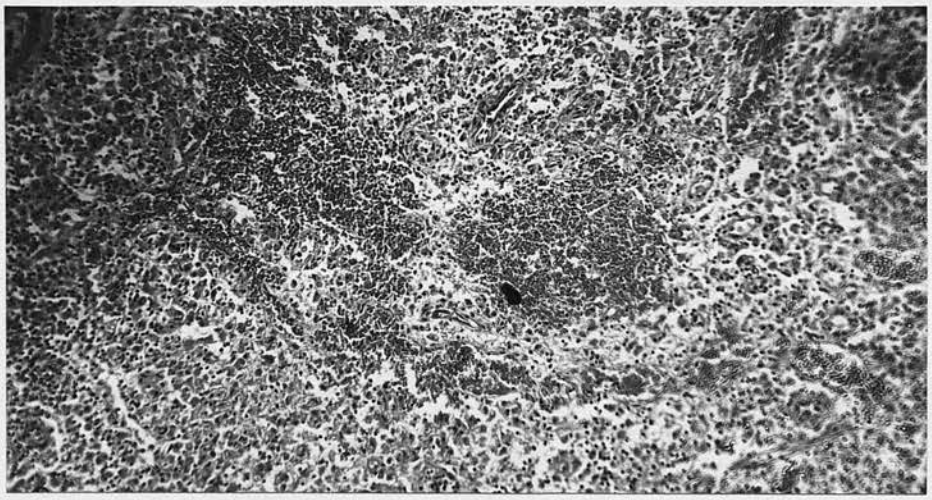

Fig. 33. Case H. 7. Lymph node. Autopsy.
Area of haemorrhage. (H. & E. X 55).

restricted mainly to the atypical cells. Large areas of haemorrhage and of fibrinoid necrosis were common and characteristic (figs. 32, 33). The preservation of the capsule and the increase in histiocytes in the peri-nodal tissue noted by Marshall was clearly illustrated in the lymph nodes from case H. 7.

A number of the less extensively involved lymph nodes still showed preservation of the sinus pattern but in these there was considerable proliferation of littoral cells showing phagocytic activity.

The areas of infiltration in the spleens from cases Misc. 2 and H. 7 had the same features as the involved lymph nodes. In case Misc. 3 the spleen microscopically showed areas of haemorrhage and necrosis but no infiltration.

In the liver similar changes were seen in the areas of infiltration which tended to be distributed in the portal tracts (fig. 34). The Kupffer cells in areas of the liver not involved by the infiltration were actively phagocytic, many containing red blood cells. Centrilobular necrosis and fatty degeneration were also noted.

In case Misc. 2 the pancreas was invaded by extension of the disease from neighbouring glands.

The lesions noted naked eye in the lungs of case Misc. 2 showed microscopically large areas of necrosis surrounded by an indefinite cellular infiltration. It was impossible to state whether these lesions represented the same pathology as was found elsewhere, or not.

The bone marrow in case H. 7 was heavily infiltrated and little haemopoetic tissue remained (fig. 35). No characteristic changes were found in any other organs examined.

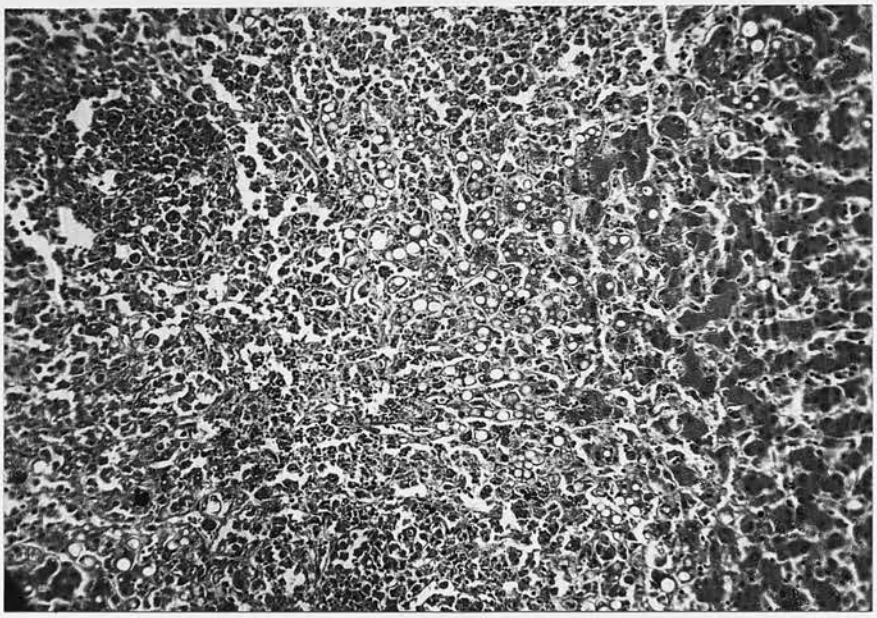

Fig. 34. Case H. 7. Liver. Infiltration with lymphocytes and histiocytes. (H. & E. X 55).

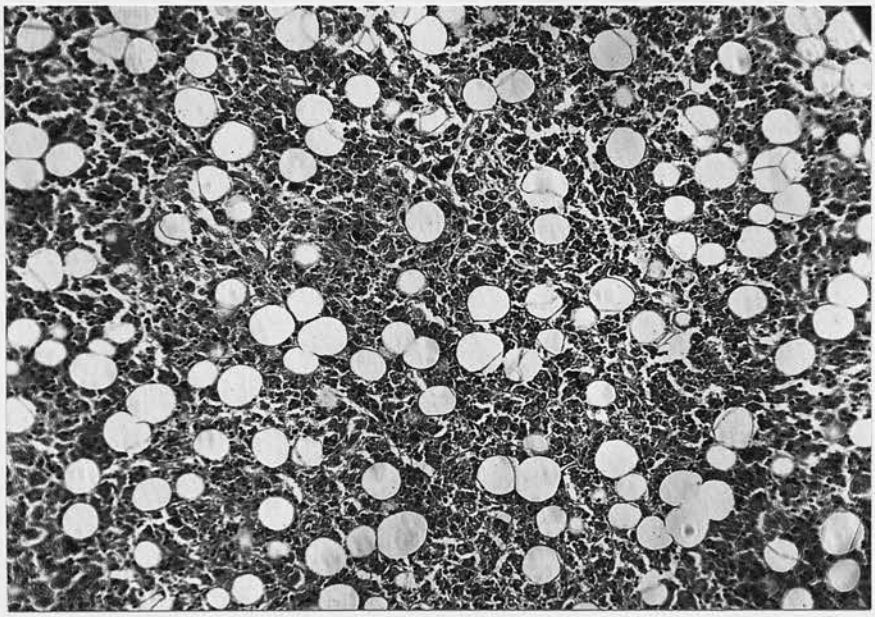

Fig. 35. Case H. 7. Bone Marrow. Replacement of haemopoeitic tissue by histiocytic proliferation. (H. & E. X 55).

III. COMMENT

The three cases described above were very similar in their behaviour and pathology to those described by Bodley-Scott and Robb-Smith and Marshall. These authors considered that histiocytic medullary reticulosis was a separate entity. There is no doubt, as Marshall admits, that other tumours of lymphoid tissue may run a course very like that found in histiocytic medullary reticulosis. In our series, for example, it would have been difficult to separate case HS. 6 (Hodgkin's sarcoma) from the three cases under discussion. Thus histiocytic medullary reticulosis cannot be diagnosed with certainty on clinical grounds for the characteristic symptoms and signs are not limited to that disease.

Many of the histological changes e.g. the proliferation of histiocytes, the erythrophagocytosis, the haemorrhages and necrosis which are so characteristic of histiocytic medullary reticulosis may be found, admittedly often not to such a marked degree and not together, in other tumours of lymphoid tumour. In histiocytic medullary reticulosis differentiation from the primitive reticular cells is predominantly to histiocytes.

The occurrence of a case (H. 7) showing transition in histology from Hodgkin's disease to histiocytic medullary reticulosis does not appear to have been described before. It suggests that, contrary to the opinion held by Bodley-Scott and Robb-Smith, there is some relationship between the two diseases. Opportunity to detect such a transition has however not been frequent as most of the published histological studies (Bodley-Scott and Robb-Smith, 1939; Marshall, 1956b) on histiocytic medullary reticulosis have been based on autopsy material alone.

Further experience is required before the status of histiocytic medullary reticulosis and its relationships to other lymphoid tumours can be defined.

CHAPTER X

LABORATORY INVESTIGATIONS

A. HAEMATOLOGICAL

I. BLOOD GROUPS

The blood groups of fifty cases are shown in table XXVIII. The ABO control series, taken from Dobson and Ikin quoted by Race and Sanger (1954), is based on figures for the United Kingdom - the population from which the army is recruited. The Rh (D) control figures quoted are also taken from Race and Sanger.

Table XXVIII

Blood Groups - 50 Cases of Lymphoid Tumours

Group	Total	A	B	AB	O	Rh+	Rh-
Reticular lymphoma	2	1	-	1	-	1	1
Hodgkin's disease	34	12	3	-	19	29	5
Hodgkin's sarcoma	3	1	-	1	1	3	-
Follicular lymphoma	3	2	-	-	1	1	2
Lymphosarcoma	5	3	-	-	2	5	-
Reticulum cell sarcoma	2	2	-	-	-	2	-
Miscellaneous	1	-	-	1	-	1	-
Total	50	21	3	3	23	42	8
Percentage	100%	42%	6%	6%	46%	84%	16%
Controls	190,177	41.7%	8.6%	3%	46.7%	84%	16%

If the series is considered as a whole the distribution of ABO and Rh blood groups is almost identical with that of the general population. The preponderance of Group O in Hodgkin's disease and of Group A in the remainder is not significant.

II. BLOOD PICTURE ON ADMISSION

(a) Haemoglobin

Unfortunately in a number of cases the haemoglobin content was recorded as a percentage without mention of the method used or of any other information which would permit conversion to grams per 100 ml. Only those cases where the results were expressed in grams per cent. have been included in the table eblow. The few female cases have been excluded.

Table XXIX

Haemoglobin in g. % on Admission

	No.	<11 g.%	11-13 g.%	13-15 g.%	>15 g.%
Reticular lymphoma	7	-	2	2	3
Hodgkin's disease	32	7	3	15	7
Hodgkin's sarcoma	4	1	1	2	-
Follicular lymphoma	3	-	-	1	2
Lymphosarcoma	6	-	-	2	4
Reticulum cell sarcoma	6	1	3	1	1

Anaemia was not a constant feature in any of the types of lymphoid tumour in the early stages.

(b) Total White Cell Count

The total white cell counts on admission are given in table XXX.

Table XXX

Total White Cell Counts per c.mm. on Admission

	No.	<4000	4-10,000	10-20,000	20-30,000
Reticular lymphoma	9	-	9	-	-
Hodgkin's disease	58	2	39	15	2
Hodgkin's sarcoma	8	1	4	3	-
Follicular lymphoma	5	1	4	-	-
Lymphosarcoma	10	-	5	4	1
Reticulum cell sarcoma	6	-	3	3	-
Mixed cell sarcoma	1	-	-	1	-

(c) Differential White Cell Count

White cells were considered to be present in abnormal numbers if the absolute counts varied appreciably from the limits of normal given by Dacie (1950).

No abnormalities were noted in the cases of reticular lymphoma.

In the cases of Hodgkin's disease and Hodgkin's sarcoma with raised total white cell counts the increase was often due to a polymorphonuclear leucocytosis. Increased eosinophil counts were only observed in eight instances, the highest being 5,300 per c.mm. (46% of a total count of 11,600 per c.mm.). Slight or moderate lymphopenia was common, but monocytosis infrequent.

No gross changes were recorded in the white cell picture of cases of follicular lymphoma on admission. A definite

lymphocytosis was however present in the peripheral blood of two cases of lymphosarcoma. The tendency for lymphosarcoma to invade the blood stream (Wiseman, 1936; Lumb, 1954; Harrison, 1956), the development of a leukaemic blood picture during the course of lymphosarcoma (Warfield and Kristjanson, 1916; Kato and Brunschwic, 1933; Gauld, 1951 and others), and the great histological similarity between lymphosarcoma and lymphatic leukaemia have led many to believe that the two conditions were merely variants of one disease. There is some evidence, however, to suggest that there is a difference in the antigenicity and hence in the chemical structure of the cells of lymphosarcoma and lymphatic leukaemia (Steinberg and Martin, 1946).

Monocytosis with the presence of abnormal cells was recorded in one case of reticulum cell sarcoma. A polymorphonuclear leucocytosis accounted for raised white cell counts in one case of reticulum cell and one case of mixed cell sarcoma.

(d) Erythrocyte Sedimentation Rate

The recorded findings are given in table XXXI.

Table XXXI

E.S.R. in 52 Cases of Lymphoid Tumours

	Number	Normal	Raised
Reticular lymphoma	1	-	1
Hodgkin's disease	37	11	26
Hodgkin's sarcoma	6	2	4
Follicular lymphoma	2	2	-
Lymphosarcoma	5	-	5
Reticulum cell sarcoma	1	-	1

III. BLOOD PICTURE DURING COURSE OF DISEASE

The routine treatment of cases of lymphoid tumour by ionising radiations, cytotoxic drugs and blood transfusion, all of which may effect the blood picture, made it difficult sometimes to decide which observed phenomena was due to disease and which to treatment. Nevertheless certain trends, none of which were specific, could be made out.

(a) Reticular Lymphoma

One of the cases of reticular lymphoma (RL. 4) which progressed to Hodgkin's disease and the case running a rapid course (RL. 7) developed anaemia.

(b) Hodgkin's Disease and Hodgkin's Sarcoma

In Hodgkin's disease the development of anaemia, if not already present on admission, was usual during the course of the disease. This anaemia was usually normochromic or hypochromic and normocytic or microcytic. Normoblasts were sometimes present in the peripheral blood. Haemolytic anaemia can occur in Hodgkin's disease (Dacie 1951). One case (H. 20) was reported to have died from haemolytic anaemia and in a further three a haemolytic mechanism was suspected.

Leucocytosis often due to an increase in polymorphs was observed to develop in a number of cases; leucopenia usually associated with therapy, was by no means uncommon. The development during the course of the disease of an eosinophilia was sometimes noted, but in only one case was the eosinophilia persistent. An absolute monocytosis occurred in three cases, but relative monocytosis at some stage was fairly frequent. Monocytosis has often been

reported in Hodgkin's disease (Stewart, 1921; Wiseman, 1936; Bessis, 1948; Wintrobe, 1951; Whitby and Britton, 1953). The appearance of abnormal mononuclear cells and of myelocytes in the peripheral blood was occasionally noted.

Thrombocytopenia was sometimes observed especially in patients receiving cytotoxic drugs. In one patient the platelet count was increased. Abnormal particles thought to be parts of megakaryocytes (Bunting, 1911) and megakaryocytes themselves (Minot, 1922) have been reported in the blood in Hodgkin's disease, but these were not observed in this series.

The changes seen during the course of Hodgkin's sarcoma paralleled those seen in Hodgkin's disease. Abnormal mononuclear cells appeared in the blood of one patient (HS. 6) towards the end of her illness and the finding of tumour cells in the vessels of lymph nodes at autopsy has already been described.

The findings therefore in this series support the conclusion that the changes found in the blood in Hodgkin's disease are neither characteristic nor diagnostic (Roth and Watkins, 1936; Kracke, 1941; Whitby and Britton, 1953 and others).

(c) Follicular Lymphoma

One case (FL. 1) developed anaemia severe enough to require transfusion.

In a second patient (FL. 6) atypical monocytes appeared in the peripheral film and these were found in sufficient numbers (up to 52%) to suggest the possibility of aleukaemic leukaemia. At this time he was found to have thrombocytopenia (20-40,000 per c.mm.) but no anaemia. Splenectomy was followed by a rise of platelets to

normal but the atypical cells in his blood persisted and were still present on his discharge from the army. Earlier workers (Brill et al., 1925; Baehr and Rosenthal, 1927) found no changes in the white cells in follicular lymphoma but later reports (Gall et al., 1941; Wintrobe, 1951) refer to the presence of atypical cells in the peripheral blood.

(d) Lymphosarcoma

Anaemia developed frequently. The most interesting changes were in the white cells. Primitive cells of the lymphocyte series appeared in the peripheral circulation in three cases - including one of the two cases noted as having a distinct lymphocytosis on admission. The second case in which a raised count was noted on admission continued to manifest a lymphocytosis but primitive cells were not observed in the blood. The relationship between lymphatic leukaemia and lymphosarcoma has already been mentioned.

(e) Reticulum Cell Sarcoma and Mixed Cell Sarcoma

The changes noted were of a non-specific nature. Leucopenia was seen several times but only in patients who had received nitrogen mustards. The association of reticulum cell sarcoma with a leukaemic blood picture (Richter, 1927, 1928; Edling, 1938) was not seen in these cases included in this series. Recently, however, a case was treated in the Queen Alexandra Military Hospital which histologically from the autopsy material would be classified as a reticulum cell sarcoma and which in life showed a blood and marrow picture of acute aleukaemic leukaemia.

IV. BONE MARROW

Many of the bone marrow biopsies included in this series were performed by the author but for a number of the cases prior to 1953 it was necessary to rely on the notes for reports of marrow findings.

(a) Reticular lymphoma

The marrow was normal in all six cases examined.

(b) Hodgkin's disease

Twenty-six marrow biopsies were performed on twenty-three patients in varying stages of the disease. Fifteen of the twenty-six marrow pictures were within normal limits. Of the marrows which could be considered abnormal one showed complete aplasia (biopsy performed two months before death), the remainder normal or increased cellularity.

In two instances there was evidence of maturation arrest in the erythrocyte series; in another two there was normoblastic hyperplasia.

The most frequent change noted was an increase in the number of plasma cells (eight cases) and reticulum cells (six cases - nine biopsies). Increase in eosinophil myelocytes and eosinophils was a feature of only six marrow biopsies (five patients). Megakaryocytes were present in increased numbers in three biopsies.

These non-specific and inconstant findings are in general agreement with many previously published (Morrison and Samwick, 1939; Limarzi and Paul, 1948, 1949; Cooper and Watkins, 1949; Leitner, 1949).

The diagnosis of Hodgkin's disease by bone marrow biopsy is only possible if the specific multinucleated cells can be

demonstrated. The finding of these specific cells in bone marrow smears has been reported only on rare occasions (Varadi, 1938, 1955; Bayrd et al., 1954). Steiner (1943) has shown that although the marrow is involved in a very high proportion of cases of Hodgkin's disease the lesions are often microscopical and thus may easily be missed during biopsy. He also suggested that the involved areas may be firmer than the surrounding marrow and thus less easily aspirated.

Megakaryocytes may be confused with the multinucleated cells of Hodgkin's disease (Cooper and Watkins, 1949). A study of imprint smears of Hodgkin's lymph nodes by the methods described by Rebuck (1947) and Berman (1953) permits one to become familiar with the appearance of the freshly fixed and stained cells of Hodgkin's disease. Megakaryocytes and multinucleated cells of Hodgkin's disease can also be distinguished in sections by P.A.S. staining, the cytoplasm of megakaryocytes being strongly positive while that of the multinucleated tumour cells is negative.

Neither in smears nor in sections of the bone marrows examined were any of the characteristic multinucleated cells of Hodgkin's disease demonstrated.

(c) Hodgkin's sarcoma

There were four marrow biopsies (from three patients). Two were normal. Two (from the same patient) showed maturation arrest of the red cell series and in one of these there were also toxic changes in the myelocytes and much erythrophagocytosis by histiocytic cells. Specific multinucleated cells were not found.

(d) Follicular lymphoma

Of four marrows examined only one showed any deviation from normal and in this one, from the patient with atypical cells in his blood, abnormal mononuclear cells were seen in relatively small numbers.

(e) Lymphosarcoma

Bone marrow biopsies were performed on six patients. In one case three attempts at bone marrow biopsy were unsuccessful. Four marrows were normal including one from a patient showing an increase in small lymphocytes in the peripheral blood. A bone marrow from one of the cases in which primitive lymphocytes were found in the blood did, however, show a marked increase in cells of the lymphocyte series.

(f) Reticulum cell sarcoma

Of four marrows examined two were normal, one showed an increase in reticulum cells and one an increase in plasma cells but these changes were no more marked than the similar changes in the Hodgkin's disease cases.

(g) Summary

The alterations seen in the marrow in cases of lymphatic tumours were neither characteristic nor diagnostic.

V. PAUL-BUNNELL TEST

In a proportion of cases it was necessary as a preliminary step in the diagnosis to exclude the possibility of glandular fever. To this end a number of tests for heterophil antibody (Paul and Bunnell, 1932) were carried out. In all there were records of this being done in twenty-seven patients, often on several occasions.

In two instances a significant titre was obtained but in neither is it certain that absorption tests were included and the results were therefore not necessarily diagnostic of glandular fever; they appear to have proved misleading at the time.

B. BIOCHEMICAL

I. LIVER FUNCTION TESTS

We have seen that jaundice was not an infrequent manifestation in patients in the Hodgkin's group and was a feature of the cases of 'histiocytic medullary reticulosis'.

The liver function tests normally carried out were serum bilirubin, thymol turbidity and flocculation and serum alkaline phosphatase. Using the criteria of MacLagan (1951) to interpret the results it was found that most fell into the equivocal group while a few were clearly examples of non-obstructive jaundice. Obstructive jaundice due to enlarged lymph nodes at the hilum of the liver is said to be very rare in lymphoid tumours (Sherlock, 1955). The one case (H. 7), however, in which the liver function tests indicated obstruction, was found to have a mass of glands in the porta hepatis at autopsy.

II. SERUM PROTEINS

As many sera as possible were examined by paper electrophoresis. The results obtained are tabulated in Appendix 2 and the changes found are consolidated in table XXXII. The normal range for the method employed in Eastern Command laboratory was established by Hughes and French (1956) using sera from ninety-seven healthy individuals.

Table XXXII

Changes in Electrophoretic Patterns

Change	Total Number	Total Protein		Albumin		Globulins								No Abnormality
						α^1		α^2		β		γ		
		+	-	+	-	+	-	+	-	+	-	+	-	
Reticular lymphoma	3	-	-	-	-	-	-	-	-	-	-	-	-	3
Hodgkin's disease	16	1	2	-	7	2	-	7	-	1	-	2	1	5
Hodgkin's sarcoma	1	-	1	-	1	-	-	1	-	-	-	-	1	-
Follicular lymphoma	1	-	-	-	-	-	-	-	-	-	-	-	-	1
Lymphosarcoma	3	-	-	-	1	1	-	1	-	-	-	-	-	2
Reticulum cell sarcoma	2	-	2	-	1	-	-	-	-	-	-	-	1	-
Miscellaneous	1	-	-	-	-	-	-	1	-	-	-	-	-	-
TOTAL	27	1	5	-	10	3	-	10	-	1	-	2	3	11

+ = increased
- = decreased
} beyond normal range.

Changes in serum proteins were thus demonstrated in over half of the specimens examined. The principal changes - a decrease in total protein, a decrease in albumin, an increase in α globulins and a change in either direction of the γ globulins - are similar to those found by Luetscher (1941), Rottino et al. (1948), Peterman et al. (1948), Mider et al. (1950), Arends et al. (1954), Neely and Neill (1956) and Penman (1956). These alterations are not specific and do not differ significantly from those reported in other cancers (Mider et al., 1950; Winzler, 1953; Kay, 1954; Stewart and French, 1956).

C. IMMUNOLOGICAL

MANTOUX TEST

It is frequently stated that there is a deficient response to antigenic stimulation in patients suffering from Hodgkin's disease and allied conditions. Evans (1948), for example, inoculated patients suffering from follicular lymphoma and Hodgkin's disease with a suspension of S. paratyphi A. and found that the agglutinin response was very poor. This he attributed to the degree of disorganisation of the lymph glands.

The Mantoux test measures hypersensitivity to tuberculin. Although hypersensitivity is not synonymous with immunity it is nevertheless a manifestation of antigen - antibody reaction. Parker et al. (1932) carried out tuberculin tests in a series of patients with Hodgkin's disease and 'malignant lymphoma' and obtained fewer positive results than in normal controls. Dubin (1947) found a state of anergy to tuberculin in 38 cases of Hodgkin's disease - only one positive result being found. Paterson and Paterson (1954) on the other hand, stated that the Mantoux test was positive in many cases of Hodgkin's disease. The results of Mantoux tests on patients in the present series are given in table XXXIII. In most cases 1 in 1000 tuberculin was used but in a few instances the strength was 1 in 10,000 or 1 in 100.

Table XXXIII

Mantoux Tests in 25 Cases of Lymphoid Tumours

	Number	Positive	Negative
Reticular lymphoma	1	-	1
Hodgkin's disease	17 (100%)	12 (70%)	5 (30%)
Hodgkin's sarcoma	2	-	2
Follicular lymphoma	2	1	1
Lymphosarcoma	2	1	1
Reticulum cell sarcoma	1	1	-
TOTAL	25 (100%)	15 (60%)	10 (40%)

In the present series the proportion of Mantoux negative reactors in Hodgkin's disease (30%) was almost the same as and in the whole group (40%) somewhat higher than that found by Warrack (1950) in fit soldiers. He tested 5,000 troops and found 32% to be Mantoux negative to 1 in 100 tuberculin. Had all the cases included in table XXXIII above been tested with 1 in 100 tuberculin the percentage of negative reactors might have been slightly lower.

CHAPTER XI

DIAGNOSIS

A diagnosis of lymphoid tumour can only be established with certainty by biopsy. Before discussing the problems of histological identification, however, a few remarks will be devoted to some of the other conditions which were suggested clinically when the patients were first seen and mention will be made of the laboratory procedures carried out to exclude these possibilities.

A. CLINICAL DIAGNOSIS

Leukaemia was usually excluded on admission by examination of the peripheral blood but a few cases were seen where the distinction between leukaemia and tumour of lymphoid tissue was not obvious even after bone marrow biopsy.

Cases presenting with a large mass of rubbery glands in at least one supraclavicular fossa, an enlarged mediastinal shadow on X-ray and a blood count not grossly abnormal were usually correctly diagnosed as Hodgkin's disease on first examination.

Not all cases of Hodgkin's disease showed this characteristic clinical picture on admission. Where the lymphadenopathy was less typical the differentiation of Hodgkin's disease from the other primary lymphoid tumours, from secondary tumours and from non-neoplastic diseases became much more difficult without biopsy.

Lymphadenopathy, especially if fever was present sometimes suggested a diagnosis of glandular fever. This disease was usually excluded by the examination of peripheral blood films and by Paul-Bunnell tests. A number of cases with fever and moderate

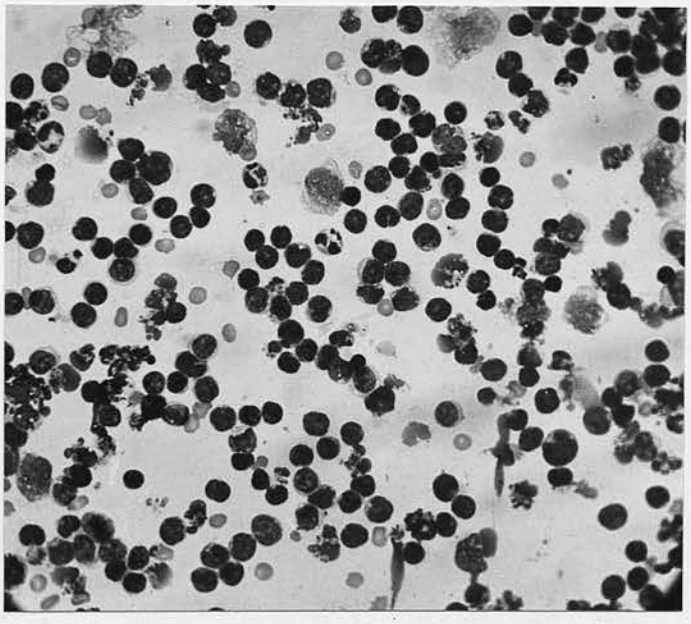

Fig. 36. Lymphosarcoma (LS. 5). Pleural fluid. Numerous cells of lymphocyte series. (Leishman X 270).

lymphadenopathy were investigated as "pyrexias of unknown origin" before biopsy was resorted to.

Tuberculous adenitis and branchial cyst featured in several cases in the differential diagnosis of a cervical swelling which on biopsy proved to be a tumour of lymphoid tissue. A diagnosis of lipoma was suggested twice on clinical examination.

As a rule the diagnosis was established quickly in those cases where superficial lymphadenopathy was present since a biopsy presented no difficulty. The same cannot be said of the patients who had no palpably enlarged glands present on admission or developing soon after admission. A number of the cases with no superficial lymphadenopathy had thoracic lesions, discovered first on X-ray examination, and these were investigated by sputum culture, radiography and bronchoscopy without success. The diagnosis was finally established by thoractomy and biopsy.

In one patient with a massive mediastinal lesion but no superficial glands, a provisional diagnosis of lymphosarcoma was made on the presence in the pleural fluid of large numbers of large and small lymphocytes. This diagnosis was ultimately confirmed at autopsy (LS. 5, and figs. 36, 49 and 50).

The cases with no palpably enlarged glands causing the greatest diagnostic difficulties were those who were admitted as "pyrexia of unknown origin". That the pyrexia might be due to some tropical disease had to be borne in mind if the individual had served overseas. In the investigation of these patients blood counts were performed; blood films examined for abnormal cells, for malaria and other protozoal parasites, for spirochaetes of relapsing

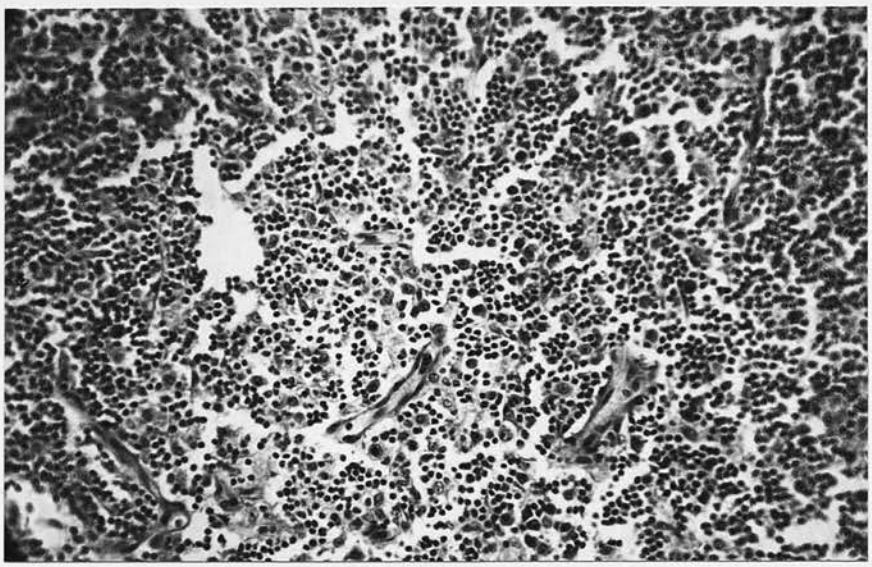

Fig. 37. Lymph node. Improperly prepared section giving impression of diffuse neoplasm. (H. & E. X 110).

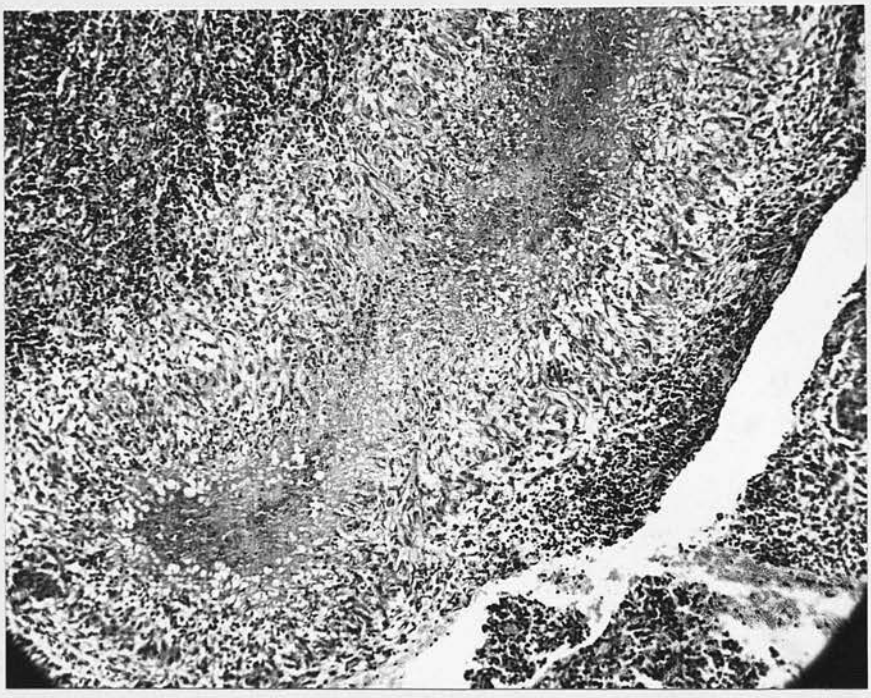

Fig. 38. Lymph node. Repeat biopsy from same site as first biopsy (Fig. 37). Tuberculosis only. (H. & E. X 55).

fever and for microfilaria; blood cultured for the enteric group, brucella and other organisms; urine examined for evidence of urinary tract infection; serum tested for enteric and brucella agglutinins and for heterophil antibody; sputum examined for tubercle bacilli and stools examined for amoebae and other intestinal parasites. During the period of investigation and observation it sometimes became apparent that the temperature was Pel-Ebstein in character and this, especially if the temperature was unaffected by antibiotics and if all other investigations were repeatedly negative, pointed towards a diagnosis of a lymphoid tumour, with Hodgkin's disease or Hodgkin's sarcoma the most likely. In one or two cases the eventual appearance of an enlarged lymph node permitted a successful biopsy to be made. In one (HS. 3) the diagnosis was finally established by splenectomy.

B. HISTOLOGICAL DIAGNOSIS

The first essential in the histological examination of a lymph node biopsy is the preparation of a good section. To achieve this the biopsy must be performed without damage to the specimen; the gland must be cut longitudinally through the hilum; fixation must be adequate; the block must be properly prepared and a thin section cut and expertly stained. Lymph node biopsies are regarded by many pathologists as among the most difficult sections to interpret. While there is good cause for this belief the fact remains that a well prepared section can do much to reduce the difficulties sometimes encountered. A bad section may not only be difficult to interpret; it may even mislead one into making an incorrect diagnosis as happened in the following case :-

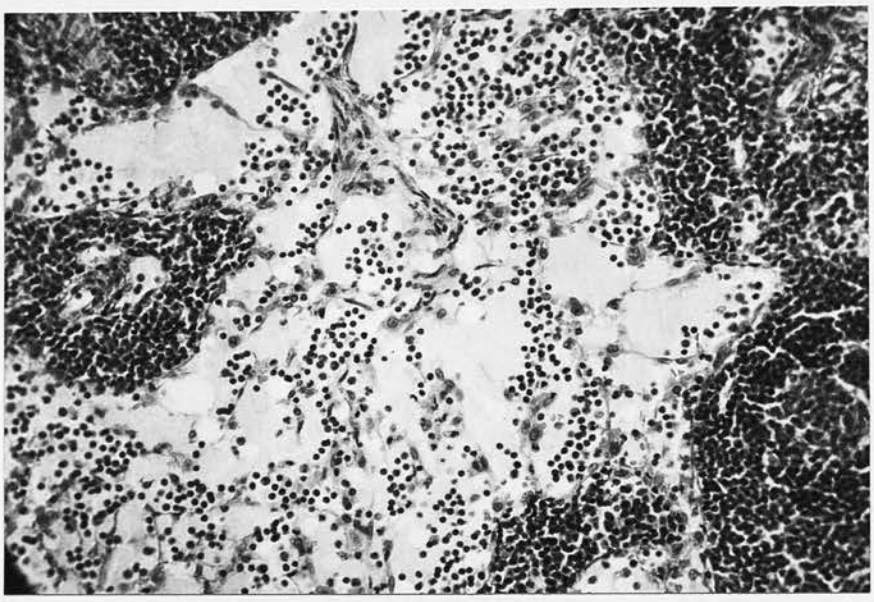

Fig. 39. Lymph node. Sinus catarrh. Dilatation of sinuses. Lymph node draining non-specific inflammatory lesion of intestine. (H. & E. X 110).

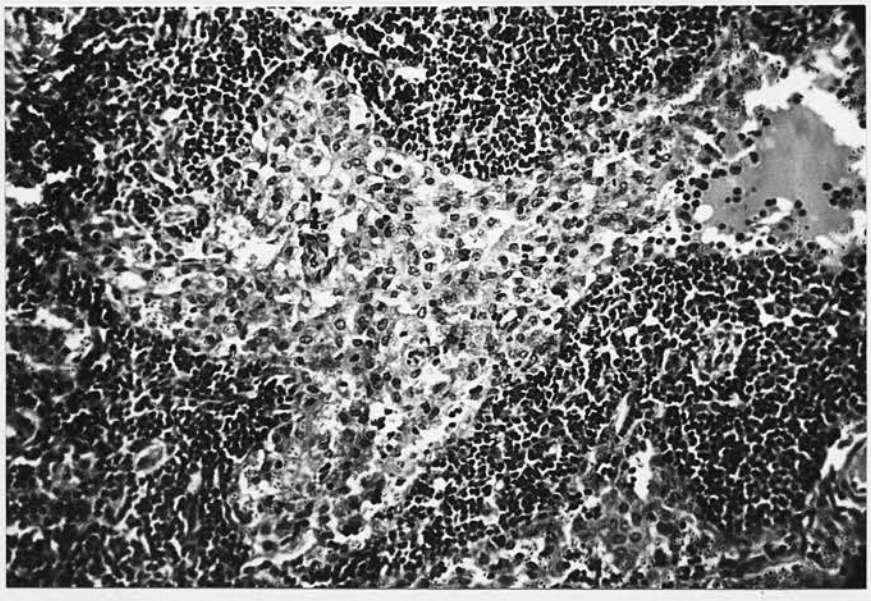

Fig. 40. Lymph node. Sinus catarrh. Proliferation of littoral cells. Lymph node from a radical mastectomy for carcinoma of breast. (H. & E. X 110).

"A young officer was evacuated to the United Kingdom with a diagnosis of malignant tumour of lymph node made on a poorly prepared section (fig. 37). Examination of the section sent from overseas with the patient suggested that the lesion was neoplastic but a repeat biopsy performed at Millbank showed only tuberculosis (fig. 38). The patient made a complete recovery on anti-tuberculous drugs."

There are many conditions in which lymphadenopathy is found and these must be distinguished microscopically from primary tumours of lymphoid tissue. Mention will only be made of lesions which have been studied personally during a review of the material available from Army sources.

Lymph nodes draining areas of tissue involved in a variety of lesions e.g. bacterial infections and neoplasms often show either one or both of two types of non-specific reaction.

(1) Sinus Catarrh in which there is dilatation and distension of the sinuses by lymph and proliferation of the littoral cells with the result that the sinuses become very prominent (figs. 39, 40). The proliferation of the littoral cells may fill the sinuses. This type of reaction must not be confused with carcinomatous invasion which occurs first in the sinuses.

(2) Reactive hyperplasia in which there is an increase in the number and size of the lymph follicles with their paler staining centres of lymphoblasts, primitive reticular cells and numerous macrophages with ingested nuclear debris (fig. 41). Mitotic activity is

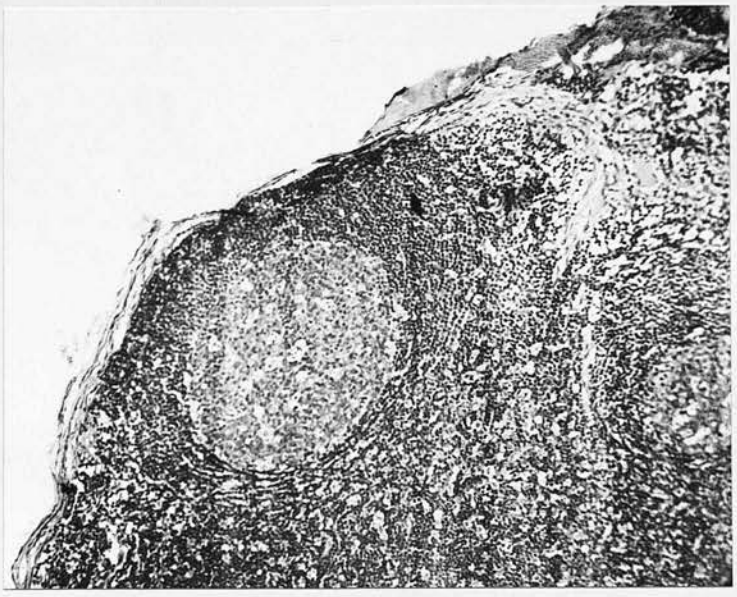

Fig. 41. Lymph node. Reactive hyperplasia. Enlarged follicle at periphery of a node draining an area of acute inflammation. (H. & E. X 55).

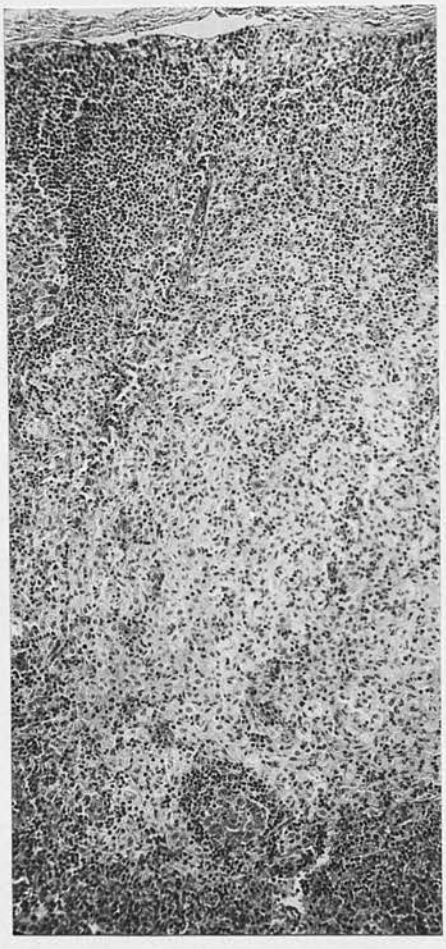

Fig. 42. Lymph node. Lipo-melanic reticulosis. Marked proliferation of littoral cells towards the periphery of the node. (H. & E. X 55).

usually marked in the centre of reactive follicles. This numerical and dimensional increase in follicles is seen in the reactive hyperplasia and in follicular lymphoma. The differentiation between the two types of follicle is said by Marshall (1956a) to present little difficulty, but a study of the army material supports the view held by Harrison (1956), Wright (1956b) and Rappaport et al. (1956) that sometimes it may be very difficult, if not impossible to distinguish between the two. In fact one must agree with Wetherley-Mein et al. (1952) when they state that the diagnosis may only become apparent in retrospect. In attempting to come to a decision on the nature of a follicular hyperplasia the following changes favour a neoplastic origin :-

(i) Obliteration of the sinuses.

(ii) Condensation of reticulin fibres around the follicle.

(iii) Scarcity of mitoses.

(iv) Lack of macrophages with ingested nuclear material.

A much less commonly seen proliferative lesion is that referred to as 'lipo-melanic reticulosis'. In this condition there is a very marked proliferation of the sinus littoral cells some of which can be shown to contain lipoid and melanin. This littoral cell proliferation is seen mainly towards the periphery of the node (fig. 42). Lymph nodes showing this picture are found in patients suffering from chronic skin disease usually enfoliative dermatitis. Lipo-melanic reticulosis associated with exfoliative dermatitis must be distinguished from Hodgkin's disease with exfoliative dermatitis.

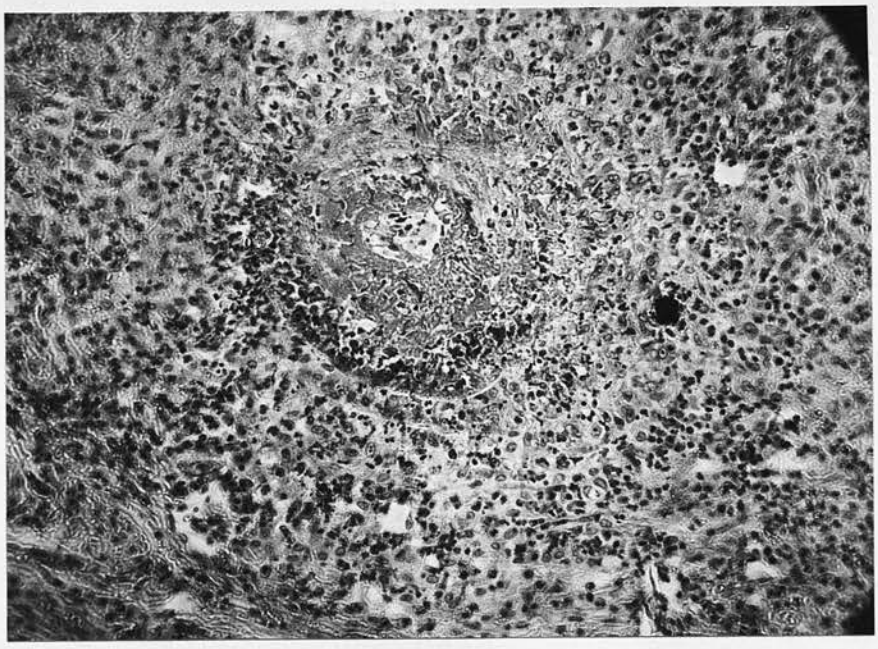

Fig. 43. Lymph node. Periarteritis nodosa. Artery in hilum of lymph node. Fibrinoid necrosis and infiltration of inflammatory cells including eosinophils. (H. & E. X 110).

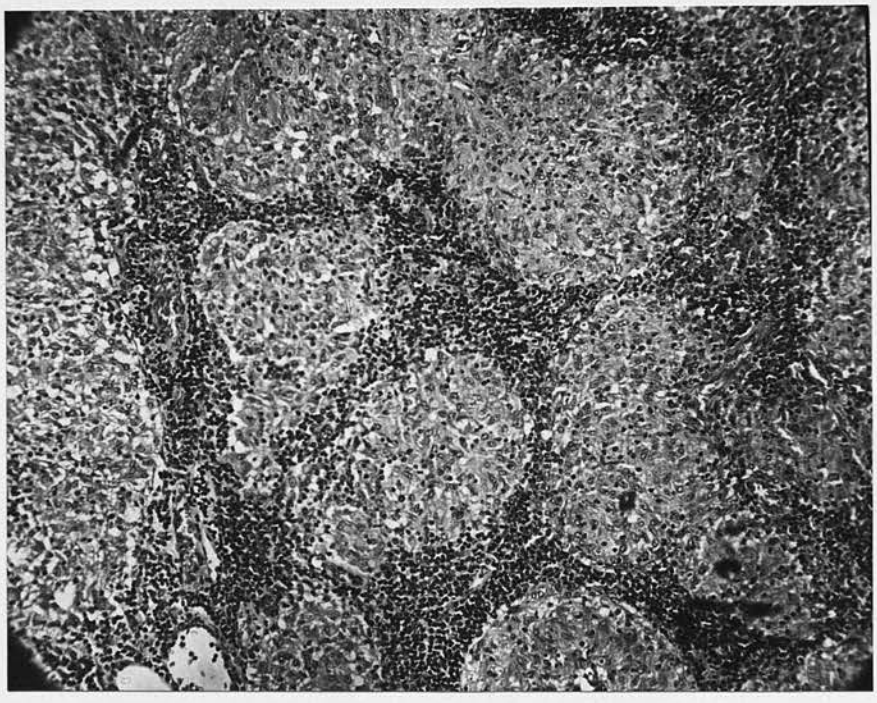

Fig. 44. Lymph node. Sarcoidosis. Focal collection of epithelioid cells. No caseation. (H. & E. X 55).

Of the common inflammatory lesions acute lymphadenitis is unlikely to give rise to much confusion. Chronic lymphadenitis especially if fibrosis is present may closely resemble Hodgkin's disease. Many cell types are common to both processes. When faced with the problem of distinguishing between these two conditions it is important to remember that a diagnosis of Hodgkin's disease should not be made unless the typical multinucleated cells are found. Small binucleated cells unlike those of Hodgkin's disease may be found in inflammatory glands and in other non-neoplastic diseases. Care should also be taken not to mistake tangentially cut blood vessels for Reed-Sternberg cells.

The importance of finding typical multinucleated cells before making a diagnosis of Hodgkin's disease cannot be emphasised too strongly. No other single feature is reliable. Eosinophilia, for example, was found in lymph nodes in lymphadenitis, in lipo-melanic reticulosis, in filariasis, in peri-arteritis nodosa (fig. 43) and in nodes draining a carcinoma of the breast.

Of the specific inflammatory disease of lymph nodes tuberculosis is the commonest. Caseating tuberculosis can be readily recognised and even the tubercles of non-caseating tuberculosis and the somewhat similar follicles of sarcoid (fig. 44) are unlikely to be diagnosed as neoplasms. The possibility that Hodgkin's disease and tuberculosis may co-exist in a lymph node must not be overlooked.

Lymphogranuloma inguinale with its micro-abscesses surrounded by epithelioid cells (fig. 45) may superficially resemble Hodgkin's disease with necrosis, but the two are easily distinguished on detailed examination.

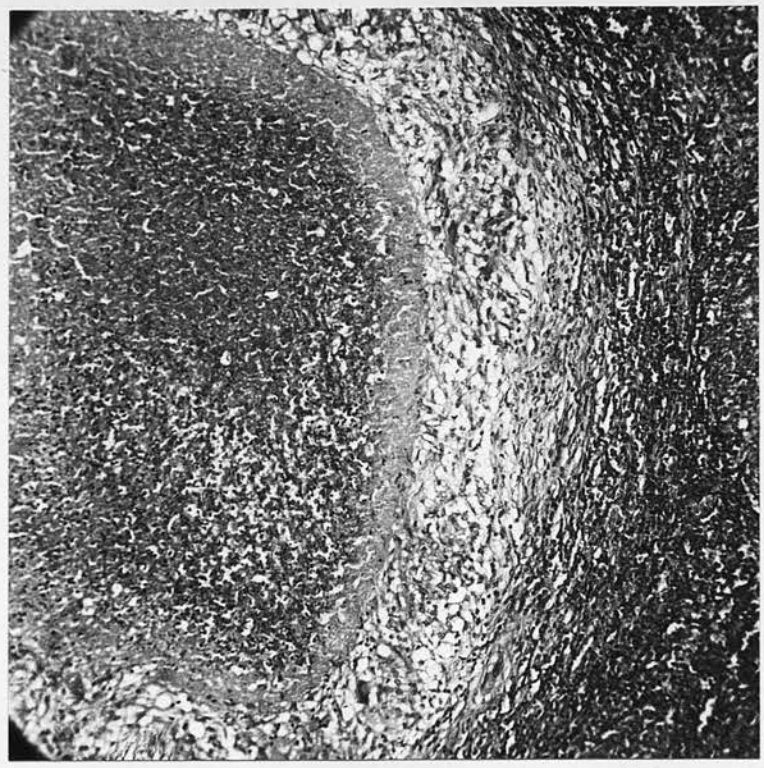

Fig. 45. Lymph node. Lymphogranuloma inguinale. Micro-abscess surrounded by epithelioid cells. (H. & E. X 55).

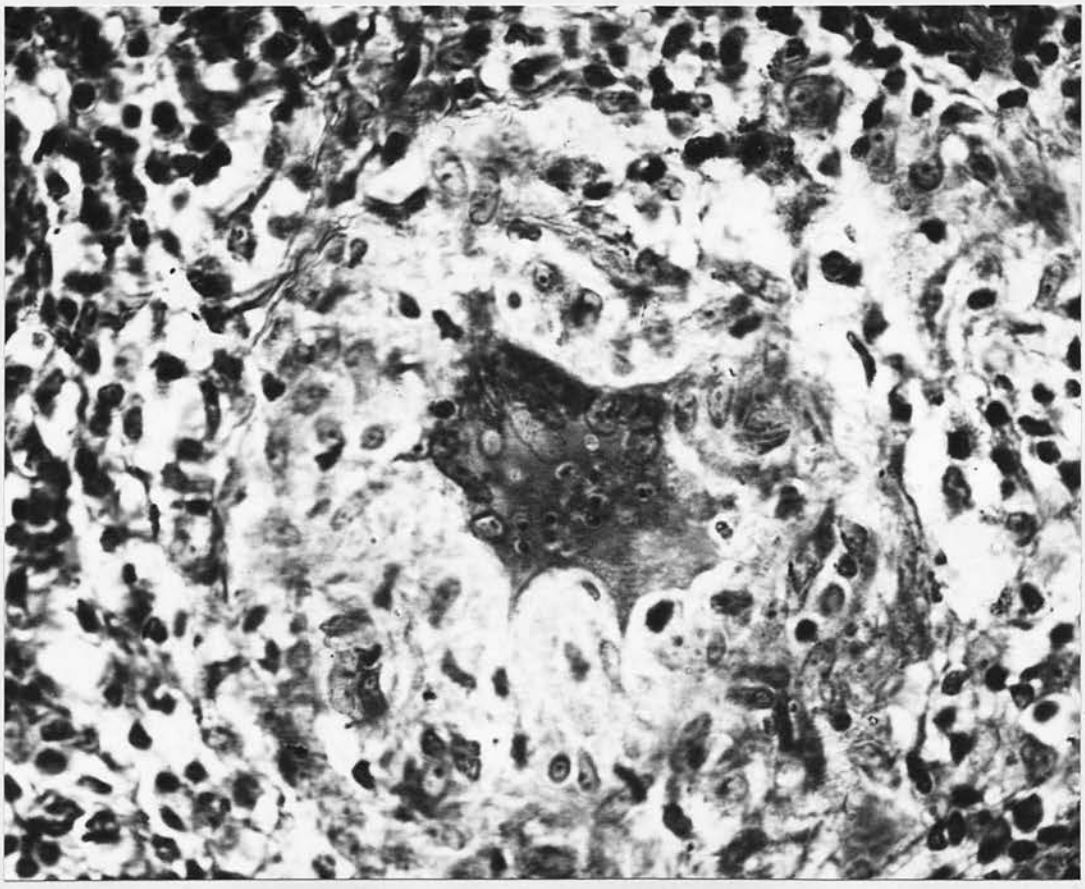

Fig. 46. Lymph node. Histoplasmosis. Giant cell with numerous Histoplasma capsulatum. (P.A.S. X 690).

Certain fungal diseases may cause lymphadenopathy. Torulosis, which can give a histological picture very similar to Hodgkin's disease, was not encountered. One gland biopsy from an East African soldier showed a marked proliferation of giant cells containing the spores of Histoplasma capsulatum (fig. 46).

Examples of lipoid storage diseases causing diagnostic problems were not seen in the army material.

So far the discussion has been directed to those diseases which must be distinguished microscopically from tumour. The neoplasms themselves must be differentiated.

In reticular lymphoma and lymphosarcoma the gland is diffusely infiltrated by lymphocytes. The invariable presence of scattered abnormal reticulum cells and multinucleated cells, the lack of mitoses in the lymphocytes and the limitation of the disease by the capsule in reticular lymphoma contrast with the sheets of lymphocytes, the increased mitotic activity and the capsular penetration in lymphosarcoma.

Follicular lymphoma is unlikely to be confused with any other neoplasm although we have seen how it may be difficult to distinguish it from reactive hyperplasia. Follicular lymphoma may progress to lymphosarcoma; rupture of the follicles and capsular invasion being evidence that such a change is taking place.

Small cell lymphosarcoma is readily recognised but large cell lymphosarcoma and reticulum cell sarcoma may resemble each other closely and mixed forms are not uncommon. It is doubtful whether the separation of reticulum cell sarcoma from lymphosarcoma has much practical value from the point of view of treatment and

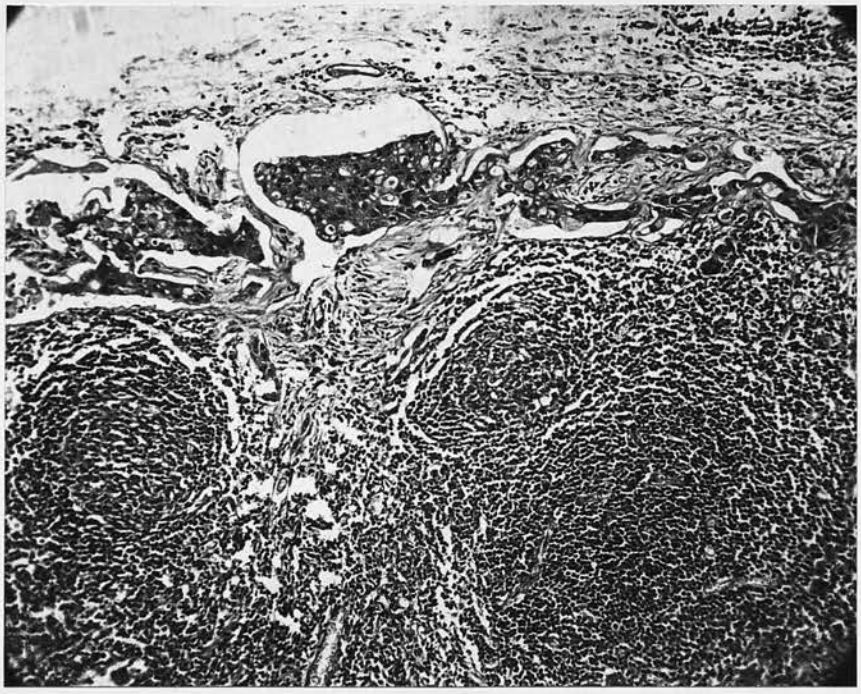

Fig. 47. Lymph node. Secondary carcinoma. Tumour in subcapsular sinus. (H. & E. X 55).

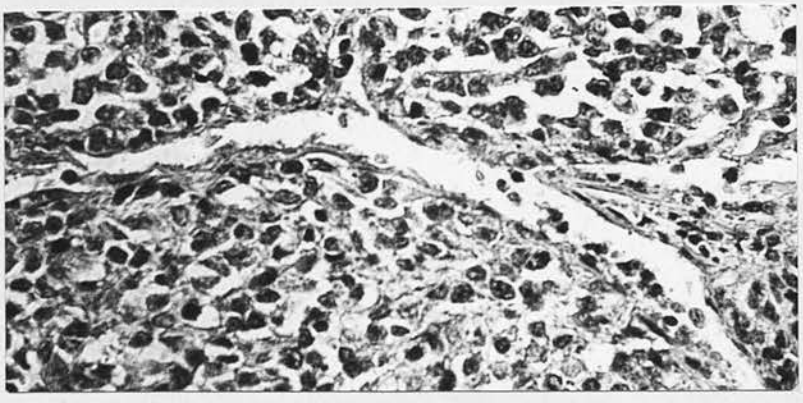

Fig. 48. Lymph node. Reticulum cell sarcoma (RCS. 1). Proliferation of tumour stretching but not invading wall of sinus. (H. & E. X 330).

prognosis. The lymph nodes of lymphosarcoma cannot be distinguished from the lymph nodes in lymphatic leukaemia.

Neuroblastoma may simulate lymphosarcoma or reticulum cell sarcoma especially when rosette formation is scanty.

The most likely source of confusion in the diagnosis of a reticulum cell sarcoma is invasion of a lymph node by secondary carcinoma. Secondary carcinoma reaches a lymph node through the afferent lymphatics and is distributed first in the subcapsular then in the medullary sinuses (fig. 47) finally invading and displacing the lymphoid tissue. The reticulum cell sarcoma on the other hand arises in lymphoid tissue. Lumb (1954) has drawn attention to the fact that it is sometimes possible to find a reticulum cell sarcoma proliferating up to and stretching the wall of a lymphatic sinus without actually invading the sinus (fig. 48) and he found this useful in differentiating primary lymphoid from metastatic tumours. Complete replacement of a lymph node by anaplastic carcinoma may be extremely difficult if not impossible to distinguish from reticulum cell sarcoma on histological grounds. Several cases were excluded from this series because the distinction between these two tumours could not be made with any degree of certainty, and more than one case was rejected because the biopsy diagnosis of reticulum cell sarcoma was proved wrong by the finding of a bronchial carcinoma at autopsy.

Many of the points in the histological diagnosis of Hodgkin's disease have been brought out earlier in the discussion on the non-neoplastic lesions of lymph nodes, for Hodgkin's disease is perhaps more likely to be confused with chronic lymphadenitis than

with say, lymphosarcoma. In Hodgkin's disease the cellular proliferation is pleomorphic and typical multinucleated cells are always present.

Finally it is perhaps worth noting that if a lymph node shows under a low magnification preservation of its normal architecture throughout it is unlikely that further detailed examination will discover any primary neoplastic process, although it may reveal small clumps of secondary tumour in the sinuses.

CHAPTER XII

TREATMENT

A detailed discussion of the treatment of patients suffering from lymphoid tumours requires special knowledge and experience not possessed by the author. No attempt will therefore be made to present a complete account of the subject.

I. SURGERY

This was usually limited to the performance of a diagnostic biopsy.

In one case of reticular lymphoma the only involved gland was completely excised and no further treatment was given (RL. 1).

In two cases of Hodgkin's disease (H. 26 and H. 50) a complete clearance of all glands in the only affected area was carried out and this was followed by a course of radiotherapy. It is interesting to note that of these two cases one was still serving in December 1955 - 6 years after operation; the second completed his military service before discharge from the army and was well in December 1955. Baker and Mann (1940) reported two cases of Hodgkin's disease in which complete excision was followed by no further evidence of disease after ten years and twelve years respectively.

One case of follicular lymphoma was treated by excision of all affected glands which were limited to one groin, followed by radiotherapy. He was alive and well four years afterwards. In another case splenectomy was performed on account of hyperplenism.

Excision of an intestinal tumour was performed in one case

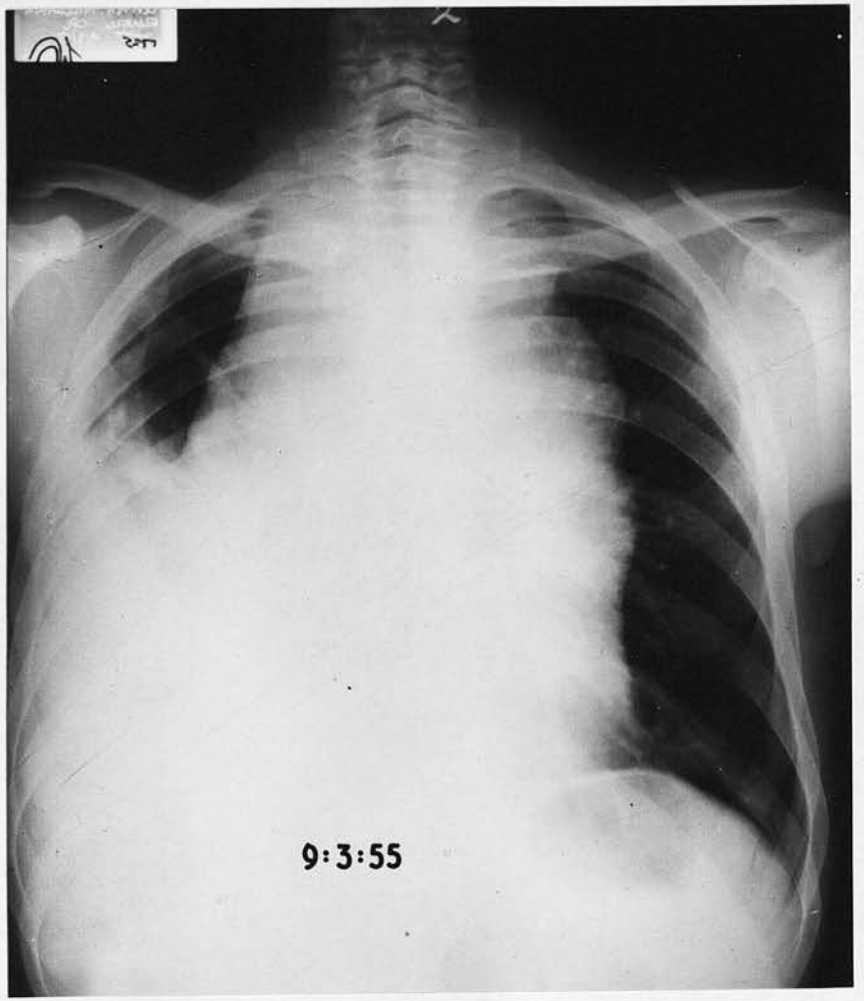

Fig. 49. Lymphosarcoma (LS. 5). Massive mediastinal tumour.(Courtesy Sir Stanford Cade).

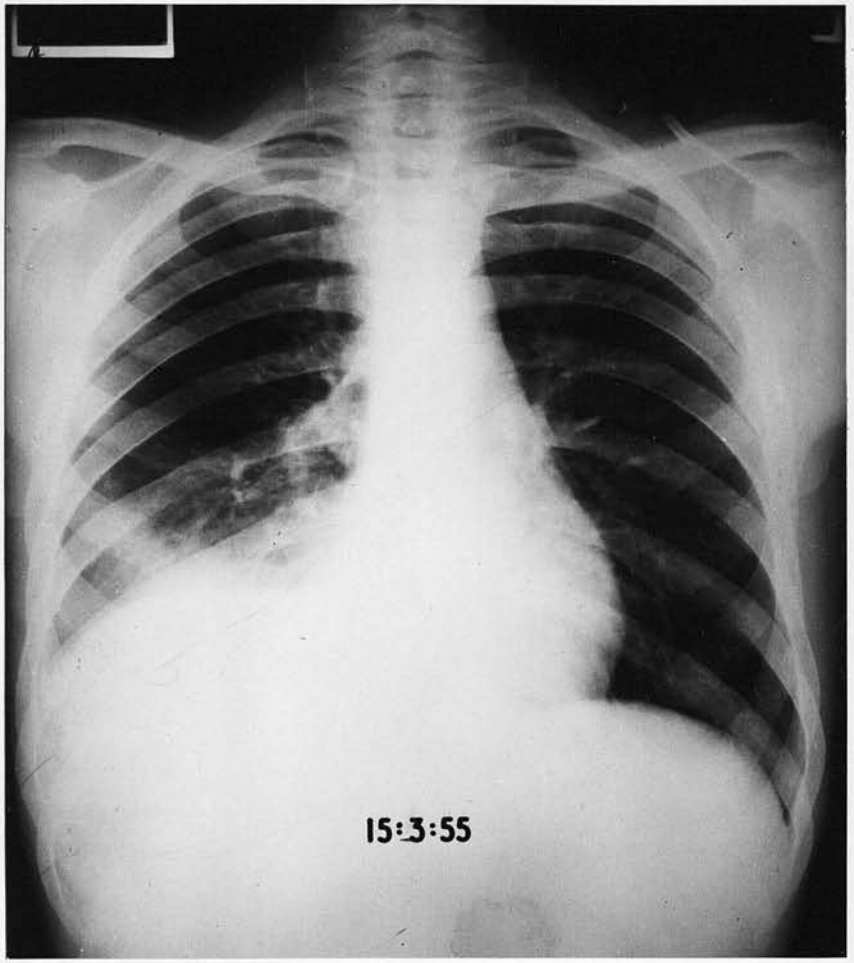

Fig. 50. Lymphosarcoma (LS. 5). Dramatic temporary effect of radiotherapy. Marked reduction in size of tumour in six days after only 600 r.

of reticulum cell sarcoma and this was followed by post operative radiotherapy to the abdomen.

II. RADIOTHERAPY

Radiotherapy is generally considered to be the treatment of choice in the first instance if the disease is still localised (Allchin, 1952; Windeyer, 1955). Many of the present series (all types of tumour) received radiotherapy to affected areas. There is a general consensus of opinion that radiotherapy causes regression of tumours and an improvement in the patients condition (Desjardins, 1932; Leucutia, 1934; Jacox et al., 1936; Gilbert, 1939; Allchin, 1952). Sometimes especially in lymphosarcoma the regression of a tumour may be dramatic (case LS. 5, figs. 49, 50.)

Radiotherapy is held by some to prolong the life of patients suffering from Hodgkin's disease (Leucutia, 1934; Jacox et al., 1936; Gilbert, 1939); others while agreeing on the benefits of radiation do not consider it prolongs life (Minot, 1926; Minot and Isaacs, 1926; O'Brien, 1941).

III. CHEMOTHERAPY

In many cases sooner or later the response to radiation became less effective and a decision to institute treatment with chemotherapy was then made. Chemotherapy was used initially also in those cases who presented with several affected areas especially if systemic manifestations were apparent.

Two cases of Hodgkin's disease received treatment with actinomycin an antibiotic used by Trounce et al. (1955) in the treatment of Hodgkin's disease. One case of Hodgkin's disease received triethylene melamine (T.E.M.). T.E.M. has been

reported as producing beneficial effects in a proportion of cases of Hodgkin's disease (Willet et al., 1951; Meyer et al., 1951 and others) but has the disadvantage of being extremely toxic to the bone marrow (Paterson et al., 1953; Nabarro, 1953; Haddow, 1953; Editorial, 1954, 1955).

Many of the patients suffering from Hodgkin's disease, Hodgkin's sarcoma, lymphosarcoma and reticulum cell sarcoma were treated with nitrogen mustards which produced improvement in many instances especially in Hodgkin's disease. The administration of nitrogen mustards is attended by certain well known drawbacks. Toxic effects include thrombosis at the site of injection, nausea, vomiting and a general depression of marrow activity (Rhoads, 1946; Wilkinson and Fletcher, 1947; Nabarro, 1949; Wilkinson, 1953; Beattie and Howells, 1954) and examples of all these undesirable results were seen in our cases.

More recently two nitrogen mustard derivatives which can be given by mouth have become available. These substances known as R. 48 and C.B. 1348 have been used in the treatment of lymphoid tumours (Matthews, 1950; Galton et al., 1955). A number of the cases in the present series received one or other of these agents.

The administration of these cyto-toxic drugs resulted in a great deal of routine work for the laboratory, for in every instance it was necessary to carry out frequent blood counts to ensure that the haemoglobin, white cell count and platelet count did not fall to a dangerous level. In a number of cases it was found necessary to suspend treatment because of bone marrow damage.

IV. BLOOD TRANSFUSION

Blood transfusion either with whole blood or packed cells was extensively used in treatment particularly in the later stages of the disease. In the case of patients repeatedly transfused it was the practice in the Queen Alexandra Military Hospital, whenever possible, to have the blood cross matched by the South London Regional Blood Transfusion Centre. By this arrangement it was possible from the large stock available, for the patient to be given blood of a group as identical as possible to his own and thus to reduce the risk of immunisation following frequent transfusions. In Eastern Command Laboratory routine facilities were available only for ABO and D grouping. There is no record of any patient in this series developing an immune antibody as the result of a blood transfusion.

V. MISCELLANEOUS

The additional measures found necessary included the use of antibiotics to combat secondary infection; the giving of streptomycin and p-aminosalicylic acid to the case of Hodgkin's disease and tuberculosis; the treatment of itching by antihistamines, phenobarbitone and methyl testosterone; the administration of iron to improve the haemoglobin level and the use of morphine to relieve pain.

CHAPTER XIII

ANALYSIS OF RESULTS AND PROGNOSIS

A. THE HODGKIN'S GROUP

The survival times of patients in the Hodgkin's group from the time of first admission to hospital are shown in tables XXXIV to VI.

Table XXXIV

Follow up of 11 Cases of Reticular Lymphoma

Survival in Years	Under 1	1-2	2-3	3-4	4-5	5-6	6-7	Over 7	Total
Alive and well	1	1	1	1	1	1	1	2	9
Alive with active disease	-	-	-	-	-	-	-	-	-
Dead	1	-	-	-	-	1	-	-	2

Table XXXV

Follow up of 63 Cases of Hodgkin's Disease

Survival in Years	Under 1	1-2	2-3	3-4	4-5	5-6	6-7	Over 7	Total
Alive and well	2	3	1	0	3	1	1	-	11
Alive with active disease	8	4	1	1	1	2	-	-	17
Dead	9	11	7	5	2	1	-	-	35

Table XXXVI

Follow up of 8 Cases of Hodgkin's Sarcoma

Survival in Years	Under 1	1-2	2-3	3-4	4-5	5-6	6-7	Total
Alive and well	-	-	-	-	-	-	-	-
Alive with active disease	-	-	-	-	-	-	-	-
Dead	5	2	1	-	-	-	-	8

The five year survival figures are given in table XXXVII. Although based on small numbers the percentage survivals correspond fairly closely with those given by Tod (1952), Paterson and Paterson (1954) and Jelliffe and Thomson (1955).

Table XXXVII

5 Year Survival Figures

	Number Eligible	Number Alive	Percentage
Reticular lymphoma	6	5	83%
Hodgkin's disease	21	5	24%
Hodgkin's sarcoma	4	0	0%

The average duration of life of the fatal cases from first admission to hospital was :-

Reticular lymphoma 3 4/12 years

Hodgkin's disease 2 years

Hodgkin's sarcoma 1 year

It is interesting to examine the survival of the cases where the biopsy was regarded histologically as being intermediate between reticular lymphoma and Hodgkin's disease or between Hodgkin's disease and Hodgkin's sarcoma (table XXXVIII).

Table XXXVIII

Survival of Intermediate Cases in Years

	Alive	Dead
Reticular lymphoma - Hodgkin's disease	4 7/12, 2/12, 4 2/12, 4 2/12, 4 3/12, 3 10/12.	1 9/12, 5 6/12.
Hodgkin's disease - Hodgkin's sarcoma	5 2/12.	7/12, 1 3/12, 10/12, 5/12.

It will be seen from table XXXVIII that the cases of Hodgkin's disease which histologically bordered on reticular lymphoma had a relatively good prognosis in most instances while those bordering on Hodgkin's sarcoma generally had a bad prognosis.

Excluding these intermediate types there was no histological feature in the ordinary case of Hodgkin's disease which could be said to have prognostic significance.

It has been stated (Craver, 1934; Bersack, 1944; Peters, 1950; Jelliffe and Thomson, 1955 and others) that generally the survival in Hodgkin's disease is longest in those cases presenting with disease which is still localised to one group of glands. In our sixty-three cases of Hodgkin's disease nineteen had only one group of glands affected and a negative chest X-ray when first seen.

Of these - eight are dead and eleven alive. The eleven alive, however, include all but one of the cases surviving at least four years.

B. FOLLICULAR LYMPHOMA

The survival times of the six cases is shown in table IXL.

Table IXL

Survival of 6 Cases of Follicular Lymphoma

Survival in Years	Under 1	1-2	2-3	3-4	4-5	5-6	6-7	Total
Alive and well	1	-	-	-	1	-	-	2
Alive with active disease	-	1	1	-	-	-	1	3
Dead	-	-	-	-	1	-	-	1

The transition of follicular lymphoma to lymphosarcoma in one case has already been noted. A study of the lymphosarcoma material (Chapter VIII) suggests that three of the cases were examples of follicular lymphoma which had become frankly malignant by the time of the first biopsy.

C. LYMPHOSARCOMA, RETICULUM CELL SARCOMA AND MIXED CELL SARCOMA

The survival figures for cases of lymphosarcoma, reticulum cell sarcoma and mixed cell sarcoma are given in table XL.

Table XL

Survival in 21 Cases of Sarcoma

Disease	Survival in years	<1	1 - 2	2 - 3	3 - 4	Total
Lymphosarcoma	Alive and well	1	1	-	-	2
	Alive with active disease	-	-	-	-	-
	Dead	9	-	-	-	9
Reticulum cell sarcoma	Alive and well	-	-	-	-	-
	Alive with active disease	1	-	-	-	1
	Dead	5	1	-	1	7
Mixed cell sarcoma	Alive and well	-	-	-	-	-
	Alive with active disease	-	-	-	-	-
	Dead	2	-	-	-	2

The average duration of life of the fatal cases was :-

Lymphosarcoma - 3 months

Reticulum cell sarcoma - 1 1/12 years

Mixed sarcoma - 1 month

The five year survival rates for all three types of sarcoma are 0% but the numbers are too small for this to have any real value. Robb-Smith (1956b) found a 15% five year survival in four hundred and fifty cases.

D. COMMENTS

The course of the disease in many of the army cases was related to the histological diagnosis of the biopsy specimen although it must be stressed that occasional exceptions were seen. The pattern which emerged from a study of these cases can be stated in general terms.

Patients with lymph node biopsies showing the histological picture of reticular lymphoma (Syn. benign Hodgkin's disease, Hodgkin's paragranuloma, early Hodgkin's disease) remained fit for many years although a proportion progressed eventually to Hodgkin's disease. Follicular lymphoma behaved similarly except that progression, when it occurred, was to lymphosarcoma.

Cases diagnosed on biopsy as Hodgkin's disease usually ran a progressive course over a period of about two years but a proportion were dead within a shorter time while others remained fit for several years. Histology was of no value on predicting prognosis in cases of Hodgkin's disease except when the histological changes were intermediate between Hodgkin's disease and either reticular lymphoma or Hodgkin's sarcoma.

A histological diagnosis of Hodgkin's sarcoma, lymphosarcoma and reticulum cell sarcoma was associated with rapid deterioration clinically. Most cases were dead within one year.

It is therefore possible for the pathologist to give some indication about the likely course of the disease but it is considered that no pathological report should go further than including a statement to the effect that "such and such a course is probable" for exceptions to the rule are by no means rare.

Linked to some extent with the problem of prognosis is the question of transition from one histological type of tumour to another. The range of transformations seen in the present series was not so extensive as, for example, that recorded by Custer and Bernhard (1948). The transition, in a proportion of cases, of reticular lymphoma to Hodgkin's disease (Jackson and Parker, 1947;

Lumb, 1954; Jelliffe and Thomson, 1955; Wright, 1956a) and in a number of cases of follicular lymphoma to lymphosarcoma (Baehr, 1932; Lumb, 1954; Wright, 1956b; Harrison, 1956) is now well recognised and further examples of these changes have been described in the preceding chapters. Alteration in the histological picture between biopsy and autopsy from Hodgkin's disease towards Hodgkin's sarcoma noted in several cases of Hodgkin's disease may be regarded as evidence of increased malignancy and anaplasia.

CHAPTER XIV

EFFECT ON MILITARY SERVICE

It is the general policy of the army to discharge from the service those individuals who are unlikely to be fit again for duty. Consequently many of the patients with lymphoid tumours were invalided and only a minority allowed to complete their engagement. The disposal of the one hundred and seven service patients is shown in table XLI.

Table XLI

Disposal of Service Cases up to December 1955

	Reticular lymphoma	Hodgkin's disease	Hodgkin's sarcoma	Follicular lymphoma	Lympho-sarcoma	Reticulum cell sarcoma	Mixed cell sarcoma	Miscellaneous	Total
Still serving	-	1	-	1	-	-	-	-	2
Completed engagement	5	5	-	2	-	-	-	-	12
Invalided from army	4	36	3	2	1	5	-	-	51
Died while serving	1	14	3	1	9	3	2	2	35
Still in military hospital	-	5	-	-	-	-	-	-	5
No record	1	-	1	-	-	-	-	-	2
TOTAL	11	61	7	6	10	8	2	2	107

The two patients still serving in December 1955 were both with their units overseas. One, a case of Hodgkin's disease, had

reached the rank of sergeant in a guards battalion six years after diagnosis; the second, a young national serviceman with follicular lymphoma, was in an infantry battalion six months after diagnosis.

It will be noted that no less than five out of eleven cases of reticular lymphoma completed their military service before discharge from the army, but only five out of sixty-one patients with Hodgkin's disease were able to do so. One third of the cases of follicular lymphoma were fit to complete their service. All cases of lymphosarcoma, reticulum cell sarcoma and mixed cell sarcoma either died while serving or were invalided.

Table XLI does not show that a small number of the patients were able to continue for a time as soldiers in a lower medical category until recurrence or progression of their disease made their discharge inevitable, or that an evan smaller number of those who died while serving were able to give some useful service before their final admission to hospital.

Three patients (RL. 4, H. 4, H. 19) illustrate a different aspect of the problem of lymphoid tumours in the army. Enquiry subsequent to their admission to a military hospital elicited the fact that all three patients had, prior to joining the army, been seen at civilian hospitals where biopsies had been performed and radiotherapy given. All three pre-enlistment biopsies were obtained. One showed reticular lymphoma (RL. 4) and two Hodgkin's disease (H. 4 and H. 19). There is little doubt that all three patients had failed to disclose the full details of their medical history on enlistment.

Much of what has been said so far deals with the effect of the disease on the individual. It is necessary now to consider briefly what problem, if any, lymphoid tumours present to the Army Medical Service.

A total of one hundred and seven histologically proven cases of lymphoid tumours in a period of eight years - an average of 3 new cases per 100,000 troops a year - does not represent a large drain on manpower. Even if all cases of lymphoid tumours were discharged as unfit for service the loss to the army would be negligible when compared with the total numbers invalided. In 1953 the latest year for which figures are available the medical discharges from all causes for male troops was 1650 per 100,000 strength (Report, 1956).

With only thirteen new cases a year a regimental medical officer is unlikely to see even one during his service; the clinicians and pathologist at a military hospital may diagnose one case each year depending on the size of the local garrison. Since the majority of cases of lymphoid tumours are evacuated to the Queen Alexandra Military Hospital the main burden of treating and caring for these patients falls on the staff of that hospital and on the staff of the Westminster Hospital where they are seen in consultation and where all radiotherapy is given.

CHAPTER XV

SUMMARY

1. The structure, histology and function of normal lymphoid tissue are described. (Chapter I).

2. The genetic relationship of the cells of lymphoid tissue is discussed. (Chapter I).

3. The history of the recognition of the various types of lymphoid tumours is traced (Chapter II) and further reviews of the published literature are given in the chapters devoted to the individual tumours. (Chapters VI - IX).

4. The neoplastic origin of the diseases included in this survey is accepted but alternative views on the aetiology of Hodgkin's disease are considered.(Chapters II and VI).

5. The evolution of the modern view that lymphoid tumours may be classified on a basis of Maximow's concept of the development of cells of reticular tissue is outlined. (Chapter II).

6. The classifications in common use are tabulated for easy reference (Table I) and the classification used detailed. (Chapter IV).

7. A plea is made for some form of agreement on nomenclature and classification. (Chapter II).

8. The history of lymphoid tumours in British military medicine is briefly reviewed. (Chapter V).

9. Lymphoid tumours are the most common malignant neoplasms in soldiers. (Chapter III).

10. There were 112 histologically proven cases of lymphoid tumour in the period 1948 - 1955 and these were distributed as follows :-

Male service personnel	-	106 cases
Female service personnel	-	1 case
Families	-	3 cases
Chelsea pensioners	-	2 cases

(Chapter V).

11. The histological classification of these tumours was :-

Reticular lymphoma	11
Hodgkin's disease	63
Hodgkin's sarcoma	8
Follicular lymphoma	6
Lymphosarcoma	11
Reticulum cell sarcoma	8
Mixed cell sarcoma	2
Miscellaneous	3

(Chapter V).

12. The incidence of lymphoid tumours in male and female service personnel has been calculated and the conclusion drawn that these tumours have no higher an incidence in the army than elsewhere and that their relative frequency is due to the age structure of the army. (Chapter V).

13. Neither rank, corps, service nor station had any significant effect on incidence. (Chapter V).

14. Each group of cases is analysed in some detail to give information on symptons on admission, duration of symptoms, physical signs on admission, the course of the disease, pathology of biopsy and autopsy material and prognosis. (Much of this information cannot be summarized). (Chapters VI - IX).

15. In general the clinical findings in the cases of reticular lymphoma, Hodgkin's disease and Hodgkin's sarcoma were similar to those reported by other authors. (Chapter VI).

16. Three of the six cases of follicular lymphoma were unusual in that they occurred in patients under the age of 25. (Chapter VII).

17. The high incidence of gastro-intestinal involvement in lymphosarcoma and reticulum cell sarcoma is remarked on. (Chapter VIII).

18. Three cases of histiocytic medullary reticulosis are included. One of these is of particular interest in that a gland biopsy taken two years before death showed Hodgkin's disease. (Chapter IX).

19. Two instances in which sequential biopsies showed transition from reticular lymphoma to Hodgkin's disease are described. A third example in a Royal Air Force patient is mentioned. (Chapter VI).

20. Eosinophils were frequently found in lymph node biopsies in Hodgkin's disease but there was no correlation between blood, marrow and tissue eosinophilia. (Chapter VI).

21. The co-existence of tuberculosis and Hodgkin's disease in the same gland was noted in the biopsy specimens from one patient only. (Chapter VI).

22. The histological distinction between Hodgkin's disease and Hodgkin's sarcoma is ill defined, the two conditions merging into each other. Autopsy material when compared with the corresponding biopsy material frequently shows in areas a more pleomorphic and sarcomatous picture. (Chapter VI).

23. The transformation of a follicular lymphoma to lymphosarcoma in one patient is recorded. (Chapters VII and VIII).

24. That in three of the cases lymphosarcoma may have arisen in a gland previously the site of a follicular lymphoma is suggested

by the finding of a definite or indefinite follicular pattern in the biopsy sections. (Chapter VIII).

25. Lymphosarcoma and reticulum cell sarcoma may closely resemble each other and mixed forms are seen. (Chapter VIII).

26. The distribution of blood groups in fifty cases of lymphoid tumours is almost identical with that of the general population. (Chapter X).

27. Haematological findings on admission and afterwards are recorded. No characteristic or diagnostic changes were found in the blood or bone marrow. (Chapter X).

28. The presence of primitive white cells in the peripheral blood in a number of cases is noted. (Chapter X).

29. Megakaryocytes can be distinguished from the giant cells of Hodgkin's disease by their reaction when stained by P.A.S., megakaryocytes being strongly P.A.S. positive. (Chapter X).

30. Changes in serum proteins as determined by paper electrophoresis were noted in over half of the cases. The alterations included a decrease of total protein, a decrease in albumin, an increase in α globulins and increase or decrease in γ globulins. (Table XXXII and Appendix 2).

31. No evidence of any significant reduction of hypersensitivity to tuberculin could be detected in patients with lymphoid tumours by the Mantoux test. (Chapter X).

32. The difficulty of diagnosing cases presenting without superficial lymphadenopathy is discussed. (Chapter XI).

33. The first essential in the histological examination of a lymphoid tumour is the preparation of a good section. (Chapter XI).

34. The histological diagnosis of lymphoid tumours is discussed. (Chapter XI).

35. Treatment is briefly described. (Chapter XII).

36. The use of cyto-toxic drugs necessitates frequent blood counts. (Chapter XII).

37. Repeated blood transfusions may become necessary and every effort should be made to prevent the development of immune anti-bodies. (Chapter XII).

38. The relationship between histology and prognosis is investigated. Cases of reticular lymphoma or follicular lymphoma have a relatively good prognosis, those of Hodgkin's sarcoma, lymphosarcoma and reticulum cell sarcoma a very bad prognosis, while those of Hodgkin's disease have an expectation of life of about two years. Exceptions to these rules are not uncommon. (Chapter XIII).

39. The effect of a diagnosis of lymphoid tumour on a soldier's military career is discussed. The majority are discharged from the army as unfit for service. (Chapter XIV).

40. Invalidings from the army on account of lymphoid tumours form only a very small proportion of the total medical discharges. (Chapter XIV).

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APPENDIX 1

PARTICULARS OF CASES

No.	Rank	Age	1st Admission	Biopsy Site	Result to Dec.1955	Autopsy	Remarks
				RETICULAR LYMPHOMA			
RL.1	Cpl.	20	4. 5.50	Cervical gland	Alive and well	-	
RL.2	Pte.	18½	18. 8.48	Axillary gland	Alive and well	-	2nd biopsy May 55 - Hodgkin's disease
RL.3	Gnr.	21	17. 5.51	Cervical gland	Alive and well	-	
RL.4	Civ.	15	Sept. 49	Cervical gland	Died 11.8.55	No record	2nd biopsy July 1953 in army - Hodgkin's disease
RL.5	Gnr.	19	Jan. 55	Groin gland	Alive and well	-	
RL.6	Lieut.	21	20. 4.53	Cervical gland	Alive and well	-	
RL.7	Tpr.	19	8.11.49	Axillary gland	Died 4.8.50	No record	
RL.8	Sgt.	43	4. 4.49	Cervical gland	Alive and well	-	
RL.9	Tpr.	20	12. 3.54	Cervical gland	Alive and well	-	
RL.10	L/Cpl.	23	23. 8.48	Groin gland	Alive and well	-	
RL.11	Spr.	19	23. 9.52	Cervical gland	Alive and well	-	
				HODGKIN'S DISEASE			
H. 1	W.O.	41	April 48	Axillary gland	Died 1.12.49	Yes	
H. 2	Lieut.	35	16. 2.50	Cervical gland	Died 25.10.51	Yes	
H. 3	Pte.	17½	2.11.48	Cervical gland	Died 1. 8.51	No	
H. 4	Sgn.	19	11. 7.53	Occipital area	Died 21.10.54	No	Previous biopsy age 16 - Hodgkin's disease
H. 5	Pte.	19	Oct. 52	Axillary gland	Died 8.10.54	No	
H. 6	Sgt.	24	6. 5.48	Site not stated	Died 13.10.51	No.	
H. 7	Pte.	18	12.10.49	Cervical gland	Died 14.10.51	Yes	P.M. - Histiocytic medullary reticulosis
H. 8	Pte.	19	12. 2.52	Cervical gland	Died 8.12.55	No record	
H. 9	Spr.	22	10. 3.51	Cervical gland	Died 26. 8.51	No	Rapid Course.
H. 10	Dvr.	27	30. 9.52	Cervical gland	Died 20. 5.54	No	
H. 11	Pte.	23	20. 1.55	Hilar gland	Alive and well	-	Detected on M.M.R.
H. 12	Pte.	?	10. 2.53	Axillary gland	Died early 1954	No	
H. 13	Pte.	34	19. 6.48	Groin gland	Died 3. 2.50	No	
H. 14	Spr.	21	17. 5.55	Cervical gland	Alive but diseased	-	
H. 15	Pte.	35	17.10.49	Cervical gland	Alive and well Dec.54	-	Not heard of since Dec. 1954.
H. 16	Sgt.	40	11.10.50	Cervical gland	Alive	-	Known to be alive. No information on condition
H. 17	Cfn.	20	8. 7.52	Cervical gland	Died 1. 4.54	No	
H. 18	Wife	34	31. 5.51	Cervical gland	Alive and well	-	Pulmonary tuberculosis age 18 - now quiescent.
H. 19	Rfn.	18	6. 3.52	-	Died 20. 4.53	-	Biopsy and radiotherapy before enlistment (Nov. 50).
H. 20	Pte.	19	Jan. 50	Cervical gland	Died 4.11.50	-	
H. 21	Cfn.	22	18.11.52	Cervical gland	Died 1. 6.53	No	
H. 22	Sgt.	24	7.11.55	Abdominal gland	Alive but diseased	-	Died in March 1956.
H. 23	Gnr.	19	2. 7.48	Cervical gland	Died 23. 7.49	Yes	
H. 24	Spr.	22	16. 2.54	Cervical gland	Died 8. 4.54	Yes	
H. 25	Tpr.	20	1. 9.54	Cervical gland	Alive but diseased	-	
H. 26	L/Cpl.	22	17. 1.50	Axillary gland	Alive and well	-	Serving in Germany with regiment Dec. 1955.
H. 27	Pte.	18	14. 6.50	Cervical gland	Alive but diseased	-	
H. 28	Cfn.	23	5. 7.54	Cervical gland	Alive and well	-	
H. 29	L/Cpl.	20	21. 3.49	Cervical gland	Died 1. 5.53	No	
H. 30	Pte.	20	11. 3.54	Cervical gland	Alive and well	-	
H. 31	Cpl.	31	1. 1.49	Cervical gland	Died 6. 8.52	Yes	Autopsy histology not seen.
H. 32	L/Cpl.	19	30. 4.53	Cervical gland	Alive but diseased	-	
H. 33	Major	36	5. 2.52	Axillary gland	Died 14. 9.54	Yes	Biopsy in 1954 also Hodgkin's disease
H. 34	Pte.	20	6.11.55	Cervical gland	Alive but diseased	-	Detected on M.M.R. Pulmonary lesion.
H. 35	L/Cpl.	21	10. 5.54	Cervical gland	Alive but diseased	-	Died 1956.
H. 36	Sgn.	18	19.10.54	Cervical gland	Alive but diseased	-	Cervical gland showed Hodgkin's disease and tuberculosis.
H. 37	Pte.	?	7. 1.52	Cervical gland	Died 2. 3.55	No	Treated originally as glandular fever.
H. 38	Pte.	19	8.11.55	Cervical gland	Still in hospital	-	
H. 39	Pte.	21	23. 9.53	Cervical gland	Died 18.12.54	Yes	
H. 40	Pte.	32	13. 2.48	Axillary gland	Died 17. 7.48	No	
H. 41	Capt.	27	22. 9.55	Cervical gland	Alive but diseased	-	

No.	Rank	Age	1st Admission	Biopsy Site	Result to Dec.1955	Autopsy	Remarks
				HODGKIN'S DISEASE (CONT.)			
H. 42	Major	37	4. 12.52	Axillary gland	Died 28. 5.54	Yes	2nd Biopsy (3/6/53) and 3rd (12/11/53) - Hodgkin's disease.
H. 43	Sgn.	19	4. 10.49	Groin gland	Died 22. 9.52	No	
H. 44	Cpl.	?	31. 3.53	Cervical gland	Alive and well	-	
H. 45	Cfn.	20	21. 2.50	Cervical gland	Died 4. 1.52	No	
H. 46	Cfn.	19	22. 5.51	Cervical gland	Alive but diseased	-	
H. 47	Rfn.	18	14. 2.54	Mediastinal gland	Alive and well	-	Discovered on X-ray for pain in chest.
H. 48	Gdsn.	20	7. 4.55	Left lung	Still in hospital	-	Discovered on X-ray for haemoptysis.
H. 49	Pte.	20	16. 5.49	Cervical gland	Died 25. 4.50	No	
H. 50	L/Bdr.	23	9.10.51	Axillary gland	Alive and well	-	
H. 51	Cfn.	19	26. 9.55	Cervical gland	Still in hospital	-	
H. 52	Pens.	75	23. 1.51	Site not stated	Died 18. 1.52	-	No active treatment given.
H. 53	Sgn.	19	22. 8.51	Cervical gland	Alive and well	-	
H. 54	Sgt.	33	4. 6.51	Hilar gland	Died 10.10.53	Yes	Discovered on chest X-ray for cough.
H. 55	Boy	16	18. 5.55	Cervical gland	Still in hospital	-	
H. 56	Pte.	20	5. 7.54	Soft tissue	Alive but diseased	-	
H. 57	Sgt.	27	6. 7.51	Cervical gland	Died 13. 5.52	Yes	
H. 58	Sgt.	22	11. 2.52	Cervical gland	Alive but diseased	-	
H. 59	L/Cpl.	20	May 51	Site not stated	Died 19. 6.53	No.	
H. 60	Gdsn.	18	22. 9.49	Cervical gland	Died 18. 3.55	No	
H. 61	Pte.	19½	10. 5.55	Cervical gland	Alive and well	-	
H. 62	Lieut.	21	28. 7.48	Cervical gland	Died 19.12.48	No	Probably had disease for considerable time before admission.
H. 63	Cfn.	22	6.10.52	Abdominal gland	Died 7. 4.53	Yes.	Laparotomy for abdominal mass.
				HODGKIN'S SARCOMA			
HS. 1	Pte.	20	19. 9.49	Cervical gland	Died 16. 5.50	Yes	
HS. 2	Major	32	June 48	Groin gland	Died 1. 7.50	No	
HS. 3	Sgt.	27	14. 1.54	Splenectomy	Died 12. 6.54	Yes	
HS. 4	W.O.	21	March 49	Cervical gland	Died 14.10.50	Yes	
HS. 5	Tpr.	22	11. 3.49	Cervical gland	Died 19. 4.50	No record	
HS. 6	Wife	32	26. 7.54	Cervical gland	Died 4. 7.55	Yes	
HS. 7	L/Cpl.	19	25. 9.52	Axillary gland	Died 25. 4.53	Yes	Diagnosed initially as glandular fever.
HS. 8	Pte.	22	5. 3.54	Abdominal gland	Died 26.12.54	Yes	Laparotomy for mass in R.I.F.
				FOLLICULAR LYMPHOMA			
FL. 1	W.O.	28	24. 1.48	Cervical gland	Died 24. 2.52	Yes	Autopsy histology - lymphosarcoma.
FL. 2	Pte.	19	30. 8.54	Groin gland	Alive but diseased	-	2nd biopsy March 56 - follicular lymphoma.
FL. 3	Sgt.	39	11. 4.49	Cervical gland	Alive	-	No information on condition.
FL. 4	Rfn.	18	28. 4.55	Cervical gland	Alive and well	-	Still serving with regiment Dec. 1955.
FL. 5	Gdsn.	18	27. 6.51	Groin gland	Alive and well	-	
FL. 6	Pte.	25	19. 8.53	Axillary gland	Alive but diseased	-	Splenectomy. Abnormal cells in blood.
				LYMPHOSARCOMA			
LS. 1	Pte.	19	23. 8.48	Caecal gland	Died 24.12.48	No record	
LS. 2	Pens.	72	2. 5.55	Cervical gland	Alive and well	-	
LS. 3	Dvr.	19	21.12.53	Cervical gland	Alive and well	-	
LS. 4	Cpl.	25	25. 9.55	None	Died 21.12.55	Yes	
LS. 5	Cpl.	23	26. 1.55	None	Died 30. 8.55	Yes	
LS. 6	Pte.	18	23. 3.50	Groin gland	Died 29. 4.50	Yes	Biopsy - chronic lymphadenitis. P.M. - lymphosarcoma.
LS. 7	Cpl.	21	8. 6.48	None	Died 12. 6.48	Yes	
LS. 8	Pte.	22	27. 6.49	Groin gland	Died 21. 6.50	No	W.R.A.C. 2nd biopsy (cervical) also lymphosarcoma.
LS. 9	Dvr.	19	17. 9.51	Groin gland	Died 24.11.51	No	
LS.10	Pte.	18½	25. 7.50	Tonsil	Died 21.10.50	Yes	Biopsy inconclusive. P.M. - lymphosarcoma.
LS.11	Tpr.	19	21. 9.54	Site not stated	Died 12. 6.55	Yes	Biopsy inconclusive. P.M. - extensive lymphosarcoma.

No.	Rank	Age	1st Admission	Biopsy Site	Result to Dec.1955	Autopsy	Remarks
				RETICULUM CELL SARCOMA			
RCS.1	Pte.	19	27. 4.49	Cervical gland	Died 25. 4.50	No	
RCS.2	Pte.	20	10. 4.51	Gland ? site	Died 22. 5.51	No	
RCS.3	Cfn.	21	1. 1.52	Axillary gland	Died 17.11.53	No	
RCS.4	W.O.	44	16. 7.55	Cervical gland	Died 1. 9.55	Yes	
RCS.5	Spr.	22	20. 3.54	Cervical gland	Died 21.12.54	No record	
RCS.6	Colonel	50	8.10.48	Jejunum	Died 29.12.51	No	
RCS.7	Cpl.	22	19. 3.51	Axillary gland	Died 2. 7.51	Yes	
RCS.8	Rfn.	19	12. 3.55	Cervical gland	Alive but diseased	-	
				MIXED CELL SARCOMA			
MCS.1	Pte.	18	7.10.50	Caecal region	Died 6.12.50	No record	
MCS.2	Pte.	31	11. 8.48	-	Died 13. 8.48	Yes	
				MISCELLANEOUS			
Misc.1	Wife	57	5.12.54	Cervical gland	Died ?. 9.55	No	
Misc.2	2/Lieut.	23	11.11.53	Palate) Cervical gland)	Died 21. 3.54	Yes	P.M. Histiocytic medullary reticulosis.
Misc.3	Pte.	24	6. 8.52	Nil.	Died 9. 9.52	Yes	P.M. Histiocytic medullary reticulosis.

Abbreviations

Pte.	=	Private	L/Bdr.	=	Lance Bombardier
Spr.	=	Sapper	L/Cpl.	=	Lance Corporal
Dvr.	=	Driver	Cpl.	=	Corporal
Rfn.	=	Rifleman	Sgt.	=	Sergeant
Gdsn.	=	Guardsman	W.O.	=	Warrant Officer
Gnr.	=	Gunner	Lieut.	=	Lieutenant
Tpr.	=	Trooper	Capt.	=	Captain
Sgn.	=	Signalman	Pens.	=	Pensioner
Cfn.	=	Craftsman	Civ.	=	Civilian
P.M.	=	Post Mortem	W.R.A.C.	=	Women's Royal Army Corps
			M.M.R.	=	Mass Miniature Radiography

APPENDIX 2

SERUM PROTEINS IN TUMOURS OF LYMPHOID TISSUE

PAPER ELECTROPHORESIS

All figures in g./100 ml.

Tumour	Case	Total Protein	Albumin	Globulins			
				α^1	α^2	β	γ
Reticular lymphoma	RL. 5	7.3	4.8	0.2	0.8	0.8	0.7
	RL. E1	7.2	4.3	0.3	0.7	0.9	1.0
	RL. E2	6.7	4.2	0.2	0.6	0.8	0.9
Hodgkin's disease	H. 11	7.2	3.6	0.2	1.0	0.9	1.5
	H. 14	7.5	4.0	0.3	0.7	0.8	1.7
	H. 22	6.6	3.3	0.2	0.7	0.6	1.8
	H. 25	6.6	2.6	0.2	1.1	1.1	1.6
	H. 25	7.4	3.2	0.3	1.7	0.9	1.3
	H. 26	6.8	3.8	0.2	0.6	1.0	1.2
	H. 38	6.7	4.1	0.9	0.6	0.6	1.3
	H. 41	6.4	3.9	0.1	0.8	0.5	1.0
	H. 51	7.2	4.2	0.1	0.6	0.9	1.4
	H. 55	8.6	4.3	0.2	1.1	1.1	1.9
	H. 58	7.3	4.3	0.3	1.0	0.7	1.0
	H. 61	6.9	3.9	0.3	0.7	0.8	1.2
	H. E1	7.1	3.0	0.4	1.0	1.3	1.4
	H. E2	6.1	3.6	0.2	0.5	0.6	1.2
	H. E4	5.0	1.9	0.7	0.8	0.8	0.8
	H. E5	7.5	5.4	0.2	1.0	0.7	0.2
Hodgkin's sarcoma	HS. 6	5.5	2.5	0.2	1.5	1.0	0.3
Follicular lymphoma	FL. E1	6.3	3.8	0.3	0.7	0.7	0.8
Lymphosarcoma	LS. 2	6.9	4.5	nil.	0.6	1.0	0.8
	LS. 5	7.1	3.3	0.5	1.6	0.6	1.1
	LS. E1	6.4	4.9	0.1	0.4	0.4	0.6
Reticulum cell sarcoma	RCS. 4	3.5	2.1	0.3	0.3	0.5	0.3
	RCS. 8	6.2	4.1	nil.	0.7	0.7	0.7
Miscellaneous	Misc. 1	6.9	4.2	nil.	1.0	0.8	0.9
Normal sera (Hughes & French 1956)	(Lowest	6.3	3.8	nil.	0.1	0.3	0.5
	(Highest	7.8	5.6	0.4	0.9	1.2	1.7