TUMOURS OF LYMPHOID TISSUE

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The first careful clinical and pathological survey of tumours arising in lymphoid tissues is attributed to Hodgkin, who presented his observations on seven cases to the Medico-Chirurgical Society of London in 1832. In 1863 Virchow described a malignant tumour affecting the lymphatic tissues under the name of lymphosarcoma and in 1893 Kundrat pointed out many differences between Hodgkin’s disease and lymphosarcoma, mainly based on microscopic appearance and on the spread of the tumours. Numerous accounts of the pathology of the disease process appeared after that; of these the most important is Sternberg’s contribution (1898) on the histological structure of lymph glands in Hodgkin’s disease. His conclusions, however, were that the condition was a manifestation of tuberculosis. In 1902 Dorothy Reed confirmed Sternberg’s findings but thought the presence of tuberculosis to be purely coincidental; she did, however, consider Hodgkin’s disease to be of inflammatory or granulomatous origin.

The study of the morbid anatomy and histology of the affected lymph nodes and of the spleen thus led to a differentiation between Hodgkin’s disease and lymphosarcoma. In addition the study of the changes in the blood and in the bone marrow established the existence of various types of leukaemia.

The majority of workers accepted the viewpoint that a sharp line of demarcation could be drawn between these conditions, but further detailed study of the disease processes suggested to some investigators that lymphosarcoma and Hodgkin’s disease were of common origin.

Warthin (1931) in a study of 506 cases of Hodgkin’s disease, aleukaemic and leukaemic lymphatic leukaemia, and mycosis fungoides, concluded that all these diseases were true blastomata differing only by degree of differentiation shown by cell types and sites of origin.

The difference of opinion as to the nature of Hodgkin’s disease remains. However, the tendency is for more and more authorities to adopt the view that a group of primary tumours of lymphoid tissue exist, varying considerably in degree of malignancy. Warthin (1931), Gall and Mallory (1942), Herbut et al. (1945), Jackson and Parker (1944, 1947) and Willis (1948), among others, maintain the unitarian theory of origin of lymph node tumours.

In 1930 and again in 1932 Roulet introduced the term ‘Retothel sarcoma,’ which was quickly adopted under the title of ‘reticulum cell sarcoma’ by pathologists all over the world as another group of lymph node tumours to add to the already recognized lymphosarcoma and Hodgkin’s disease.

Pullinger (1932) in discussing the histogenesis of lymphadenoma clarified the position considerably without actually suggesting a classification. She based her beliefs on Maximow’s theory of the multipotential capacities of that group of cells distributed as a matrix in lymphoid and myeloid tissue and in the splenic pulp. In lymph nodes it partly lines the sinuses, in the marrow and spleen it lines the venous sinuses and appears as Kupffer cells, again lining sinuses, in the liver. These cells are known as reticulum and are made up, not of well-defined units but of sponge-like syncitia from which cells appear as a result of differentiation or degeneration. Pullinger further clarified the title reticulo-endothelial system by pointing out the difference between reticulum and endothelial cells, the latter according to Maximow being lining cells capable only of reproducing themselves. Already many workers were convinced that proliferation of the reticulum cells together with the ‘giant’ and multinucleated varieties which they produce was the essential feature of Hodgkin’s disease. Belief in the multipotential productivity of primitive mesenchymal cells together with suggestive histological and clinical data made it possible to group the leukaemias and sarcomatous conditions of lymphatic tissue together with lymphadenoma under a common heading, and as a suitable title Pullinger suggested the term ‘reticulosis,’ which had already been brought forward by Ewald (1923). Ross (1933) suggested a classification based on Pullinger’s observations but sub-divided conditions into those with and without metabolic change, a somewhat artificial concept.

Later Robb-Smith (1938) further modified the
same viewpoint, distinguishing 'reticulosis' or hyperplastic conditions and 'reticuloma sarcoma' or true blastoma. The former he divided into three main groups of disease arising respectively from undifferentiated cells in lymphoid follicles, lymph sinuses and medullary pulp, whilst the latter he sub-divided according to cytological differentiation.

From the concentrated application to the problem of diseases of lymphoid tissue in the last 120 years only a few unassailable features emerge which were not obvious at the time of Hodgkin's original papers. These may be summarized as follows:

1. A group of diseases exists affecting the lympho-reticular structures which manifest themselves clinically in a similar manner, namely, enlargement of lymph nodes with or without associated splenomegaly.

2. These diseases vary in severity from the relatively benign, with a prognosis of many years, to the intensely malignant with a prognosis of a few months.

3. The essential unity of the whole group of diseases does not demand the abolition of a component sub-division based on clinical and pathological observations; indeed such grouping must always be of value in prognosis.

However, a classification must never be so complicated as to make it necessary to fit the patient and his disease into a pigeon-hole of theoretical ideas, otherwise the essential similarity of the conditions with a sometimes imperceptible merging of one variety into another will be forgotten.

It is with these features in mind that study of this group of disease is approached.

The first difficulty is one of terminology. If the names 'reticulosis' and 'reticuloma sarcoma' in the manner suggested by Robb-Smith (1938) are accepted, there is at once a sharp differentiation of generalized hyperplasia or multifocal disease from blastomatous formation. This concept, although theoretically sound, is particularly difficult to apply in practice and many examples may be quoted where Hodgkin's disease, theoretically considered as a hyperplastic condition or reticulosis, exhibits properties such as skin and capsule invasion, features highly suggestive of a true blastoma (Ginsburg, 1934). It seems unwise to adopt such a hard and fast rule when dealing with conditions of doubtful aetiology. It is suggested, therefore, that the term 'tumours of lymphoid tissue' should be used. Such a name does not imply the acceptance of an inadequately proven theory but simply states that there exists a group of diseases of lymphoid tissue which behave in the manner of blastomata. In such a group can be included all conditions which arise as a result of the proliferation of the primitive mesenchymal cells. It is believed that these cells are capable of differentiating to produce such variables as lymphocytes, histiocytes, free macrophages, sinusal lining cells and supporting fibre-bearing cells of various kinds.

Many authorities assume that all blood cells can be developed out of pluripotential mesenchymal cells, and if such a view is accepted then myeloid and monocytic leukaemia might be included in a common group with the lymphoid tumours. Some writers regard monocytic leukaemia as a very malignant proliferation of primitive cells, calling it 'stem cell leukaemia.' Such views excite great controversy at the present time and until more satisfactory evidence is forthcoming regarding the exact relationships of these conditions, myeloid and monocytic leukaemia are best discussed elsewhere. Brief mention will be made of lymphatic leukaemia in its association with lymphosarcoma.

It was much the same concept as this which led Pullinger to the recommendation of the names of 'reticulosis' but, as this word has been so much modified and abused over the years, it is thought better to abandon it. If such a general view is accepted it might be expected that, in the better differentiated tumours, cells such as lymphocytes or reticulum cells might appear.

Thus certain broad groups might be defined where such differentiation had occurred, i.e. (1) lymphocytic proliferation, (2) reticulum proliferation and (3) mixed cells proliferation, where both lymphocytes and reticulum cells together with other cells formed from the primitive mesenchymal cell occur.

Within each of these groups a relatively well or poorly differentiated picture might be found. General histological experience indicates that a relatively bad prognosis might be expected in the poorly differentiated varieties as opposed to that of a relatively good prognosis in the better differentiated cases. Further, it may not be possible to differentiate the more anaplastic types of one group from another, and if it is admitted that a close study of several areas of the same tumour may reveal different histological appearances, and that biopsies taken at different stages of the disease may not show a constant picture, there is left a loose classification allowing for much overlap but indicating general principles of clinico-pathological relationship along the same broad lines as the subdivision of carcinoma and sarcoma.

Before giving an account of individual tumours certain of the author's concepts must be repeated and some form of classification made.

These may be listed as follows:

1. The conditions under discussion are considered to be true tumours of lymphatic tissue and to present an interrelated group.

2. All the cells found in these tumours arise.
initially from primitive mesenchyme and therefore considerable diversity of cell pattern is to be expected in view of its pluripotential capacity.

3. Although many of the tumours present a mixed cytological appearance defying clear nomenclature and leading to multiplicity of names the majority have a fairly well-defined histological patternwork.

4. To these cases with constant clinico-pathological features names may be given, and it is proposed to retain those already in common use.

5. It has been found of value to represent these views by means of the following diagrammatic table (Lumb, 1952, 1954; Table 1), where poorly differentiated and often indistinguishable tumours are found at the apex and well differentiated examples of the three cytological variants are found towards the base of the triangle. It should be made clear that the better differentiated examples do not arise by transition from the more anaplastic varieties.

6. Most cases fall easily into one of the groups shown, but a particular case may occur anywhere in the triangle. During the course of the disease many cases show a tendency to anaplastic change or, in other words, a movement towards the apex of the triangle (Table 2).

In the subsequent account lymphoid tissue tumours are discussed under the following broad headings:

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**Classification of Tumours of Lymphoid Tissue**

- **Lymphocytic differentiation:**
  - (a) Lymphosarcoma (including lymphatic leukaemia).
  - (b) Follicular lymphoma.

- **Mixed cell differentiation:**
  - (a) Hodgkin's disease.
  - (b) Reticular lymphoma.

- **Reticulum cell differentiation:**
  - (a) Reticulum cell sarcoma.

- **Anaplastic sarcomata:**
  - Including all the anaplastic varieties of the above three groups.
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Table 3
Varieties of Tumours of Lymphoid Tissue
(Westminster Hospital, 1940-52)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th></th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Lymphoma</td>
<td>29 = 7.1%</td>
<td>Lymphocytic</td>
<td>108 = 26.3%</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>79 = 19.2%</td>
<td>Differentiation</td>
<td></td>
</tr>
<tr>
<td>Reticular Lymphoma</td>
<td>21 = 5.1%</td>
<td>Mixed Cell</td>
<td>211 = 51.2%</td>
</tr>
<tr>
<td>Hodgkin's Disease</td>
<td>190 = 46.1%</td>
<td>Differentiation</td>
<td></td>
</tr>
<tr>
<td>Reticulum Cell</td>
<td>21 = 5.6%</td>
<td>Reticulum Cell</td>
<td>21 = 5.6%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
<td>Differentiation</td>
<td></td>
</tr>
<tr>
<td>Anaplastic Sarcoma of</td>
<td>70 = 16.9%</td>
<td>Anaplastic Cell</td>
<td>70 = 16.9%</td>
</tr>
<tr>
<td>Lymphoid Tissue</td>
<td></td>
<td>Variants of all types</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>410 = 100%</td>
<td>Total</td>
<td>410 = 100%</td>
</tr>
</tbody>
</table>

(a) Lymphoblastic lymphosarcoma.
(b) Hodgkin's sarcoma.
(c) Anaplastic reticulum cell sarcoma.

The three titles indicated as sub-division of Group 4 may be employed, but the practice is not recommended.

The description of the individual lesions is based on the pathological material of a series of cases treated at Westminster Hospital between 1940 and 1952. Of these 410 have full clinical details together with histological sections obtained either by biopsy or on post-mortem examination or both. Table 3 shows the groups.

Lymphosarcoma

It is considered of value to retain the name lymphosarcoma as a title for those tumours composed of cells of the lymphocyte type. The best differentiated examples consisting of fully developed lymphocytes and the most poorly differentiated being made up of lymphoblasts.

Incidence. Lymphosarcoma is one of the more common tumours of lymphatic tissue. It accounted for 19.2 per cent. of Westminster Hospital's and 20 per cent. of Gall and Mallory's series.

Site, age and sex incidence. The disease appears usually in middle life or old age, but is not rare in young people and is occasionally seen in infancy. In this series males outnumbered females by two to one.

It manifests itself most commonly by large irregular tumour masses occurring frequently in the neck, mediastinum and abdomen. Lymph nodes seem to be the most common site of origin, but examples of isolated involvement of the spleen or lymphoid tissue in the gastro-intestinal tract have been seen.

Morbid anatomy and histology. The most anaplastic examples merge into the group indicated in Table 1 at the apex of the triangle. They are composed of large cells of varying shape with frequent mitoses and it may be impossible to be certain of lymphocytic differentiation. The most fully differentiated examples may show a tendency to vague follicle formation and although this feature has only rarely been observed in our cases it is mentioned as indicating the indefinite boundaries between named types in this group of diseases.

The cases commonly referred to as lymphosarcoma, however, are those where the cellular picture is relatively uniform and clearly of lymphocytic type. In lymph nodes the normal architecture is replaced by sheets of lymphocytes. The cell membranes are clear cut and the cells lie separately from each other in a minimum of intervening connective tissue (Figs. 1 and 2).

Spread and metastases. Spread occurs from the original sites to become generalized throughout the body, and a remarkable tendency is shown for the tumour cells to invade between tissue elements thus producing the most widespread penetration. In this way organs which appear to the naked eye to be normal may be found on microscopy to be extensively infiltrated. Considerable controversy has arisen in the past as to whether the mode of spread is by metastasis or whether the disease is of multifocal origin. The association of lymphatic leukaemia with lymphosarcoma is very close. Leukaemia developed in 15 per cent. of cases of lymphosarcoma in the series at Westminster Hospital; Gall and Mallory (1942) record a figure as high as 38 per cent. among their cases. It would appear that these conditions are not separable but...
FIG. 1.—Lymph node showing a uniform sheet of lymphocytes in lymphosarcoma (H. & E. × 110).

FIG. 2.—Uniform sheet of lymphocytes (H. & E. × 450).
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FIG. 3.—Well demarcated follicles in follicular lymphoma (H. & E. x 110).

indicate a stage or variety of a single disease process. Their separate consideration is a matter of clinical convenience but it should be made clear that the histological appearances of glands and other organs are indistinguishable, whether the case be leukaemic or aleukaemic.

Follicular Lymphoma

Follicular lymphoma is a condition in which the histological appearance of the tumours consists of numerous large lymph follicles of apparently normal structure. It may be regarded as the best differentiated member of the group, a fact borne out by the relatively good prognosis which obtains in this disease.

Incidence. Follicular lymphoma is a rare condition. In the series at Westminster Hospital since 1939 it accounted for 7.1 per cent. of the total of tumours of lymphoid tissue. In Gall and Mallory's series (1942) 8 per cent. were classified as follicular lymphoma.

Site, age and sex incidence. Several cases are on record where the tumour has been solitary, occurring usually in the neck in patients of the older age groups. The mass is clearly demarcated, encapsulated and of firm consistency. Such appearances may remain constant for many years but a tendency to ultimate anaplastic change is common. However, examples are recorded of cure following local excision of a single lump (Willis, 1948).

More commonly multiple enlarged lymph nodes appear, particularly in the neck, and frequently there is an associated splenomegaly. This variety of the disease is also found in the older age groups. It was first described by Brill, Baehr and Rosenthal in 1925 and later by Symmers (1938 and 1942). Males are affected twice as frequently as females.

Prognosis is relatively good as compared with other tumours of lymphoid tissue, but it is now generally agreed that as the disease progresses there is a tendency to an increase of degree of malignancy with a breakdown of follicular pattern and proliferation of primitive cells of lymphoblastic type.

Morbid anatomy and histology. The glands are firm but not hard and on cut surface are white in colour. Microscopically variation is seen between a well differentiated and an anaplastic picture both in different stages of the disease and also in different areas of the same lymph node.

Characteristically well-formed follicles of normal appearance and clear-cut outline are seen containing pale reticulum cells in their centre and a rim of lymphocytes around the periphery. This pattern is particularly well shown after silver impregnation staining methods, as reticulin is condensed by compression around the growing cell masses (Fig. 3).

Such an appearance frequently merges into areas where generalized proliferation of cells of lymphoblast type is occurring and where mitoses are frequently seen. An early histological sign
indicating worsening prognosis and anaplastic change is a loss of clear-cut outline at the edges of some of the follicles, associated with the commencement of an irregular cellular distribution (Fig. 4). It should be noted that anaplastic cellular appearances associated with a follicular pattern may be already present when cases are seen for the first time.

**Hodgkin’s Disease**

It has been decided to retain this name in view of its wide clinical use. For most workers it indicates a condition with a definite clinical picture and in the majority of cases a characteristic histological pattern.

**Pathogenesis.** Good accounts of the pathology of Hodgkin’s disease have been given by Sternberg (1898), Andrewes (1902), Reed (1902), Longcope (1903) and Pullinger (1932). It is considered that the modern view of Hodgkin’s disease as a true tumour (Warthin, 1931; Gall and Mallory, 1942; Herbut et al., 1945; Willis, 1948) is the correct one. The condition probably arises as the result of the differentiation of primitive mesenchymal cells to produce a variety of types including those of the reticulum and lymphocyte series together with cells producing fibrosis.

In the majority of cases studied a relatively constant histology is found, but a tendency to anaplastic change may become apparent as the disease progresses.

**Incidence.** Hodgkin’s disease is the commonest tumour of lymphoid tissue. Of the cases in this group at Westminster Hospital it accounts for 46.1 per cent.; in Gall and Mallory’s series 30 per cent. of the total tumours of lymphatic tissues are of this variety.

**Sex, age and site incidence.** The condition develops more commonly in males than females, though actual figures quoted to support this statement may be fallacious. For instance, at Westminster Hospital a large number of young Servicemen have been treated, thus producing a preponderance of male cases. The age groups most commonly affected are between 20 and 40 as judged from biopsy specimen, that is during life. Cases are on record at all ages, both in the young and the old. The youngest proved case in the Westminster Hospital series was three years of age and the oldest 70 years.

The condition affects lymphatic tissue throughout the body, particularly the lymph nodes and spleen. Examples of the disease remaining localized in one situation are on record.

It is usually stated that the commonest site to be first affected is the cervical group of lymph nodes. Objection has been raised to this statement on the grounds that many collections of lymphatic tissue such as those in the abdomen are not readily observed until late in the disease when they become greatly enlarged, and that the frequency of early cervical involvement may be apparent only.

Figure 4.—Disruption of follicle edges in malignant phase of follicular lymphoma. Reticulin impregnation (H. & E. × 450).
Fig. 5.—Pleomorphic cellular proliferation in Hodgkin's disease (H. & E. × 110).

Fig. 6.—Pleomorphic cellular proliferation showing binucleate giant cells in Hodgkin's disease (H. & E. × 110).
True though such criticism may be it is a fact that in a disease which eventually produces multiple lymph node involvement the early clinical appearance of enlarged cervical glands is a very common one, and at post-mortem this group of nodes is almost invariably affected.

*Morbid anatomy and histology.* The tissues affected by Hodgkin's disease present a greyish pink colour and are of rubbery consistency becoming firmer as fibrosis increases. Lymph nodes are usually discrete. The spleen is frequently affected and macroscopically shows diffuse enlargement with yellowish patches of infiltration seen on cut surface.

The histological picture is of a proliferation of mixed cell type gradually replacing the normal lymph node and producing fibrous tissue. The appearances in the lymph nodes only will be described, for these are similar to those found elsewhere in the body.

The classical histological appearances of Hodgkin's disease may be listed as follows:

(a) Destruction of normal architecture.

(b) Proliferation of reticulum cells and giant cells.

(c) Fibrosis.

(d) A common but not constant finding of granulocytes, in particular eosinophils and plasma cells (Figs. 5, 6, 7).

The proliferating reticulum cells show some particular features. They are large cells with a single well-defined nucleus in which the chromatin network is clearly seen and usually contains a well-marked nucleolus which characteristically takes up a little pink dye in routine sections stained by haematoxylin and eosin (Fig. 8).

The cytoplasm has a very faint staining capacity and this feature, taken in conjunction with the fact that vacuolation frequently takes place, may give the appearance of a cell lying in a gap or hole between the smaller round cells (Fig. 9). Syncytial strands are usually seen joining adjacent cells.

The giant cells in this condition contain from two to five nuclei and are of the same general appearance as the reticulum cells. The cytoplasm may be pale or may take up the eosinophil dyes quite markedly.

A characteristic pattern is seen when two nuclei are found in the 'mirror image' position. It would seem reasonable to assume that these cells are a malignant variation of reticulum cells and provide the characteristic proliferating cell of the disease. The significance of eosinophil proliferation is not clear. Some authors think that the presence of these cells together with others of the granulocyte series indicates a myeloid differentiation of the proliferating cells, whilst others regard them as a secondary invader cell similar to that seen in carcinoma. In view of the inconstant appearance of eosinophils in the lesion, together with the inadequate evidence for suggesting the origin of granulocytes in Hodgkin's tissue, the author tends to favour the latter explanation.

The fibrosis in Hodgkin's disease seems to be a
FIG. 8.—Sternberg Reed cells from a case of Hodgkin's disease (H. & E. × 450).

FIG. 9.—Proliferation of reticulum cells giving an appearance of cells lying in 'holes' (H. & E. × 10).
specific feature. Proliferation of the reticulum cells leads to an increased argyrophil network and subsequently collagen is laid down upon it. It might be expected that the more slow growing and better differentiated examples of this condition would show excessive fibrosis, whilst the more rapidly advancing and malignant varieties would be more cellular and anaplastic. There is considerable evidence from the material studied at Westminster Hospital that this view is correct.

Spread and metastases. As in lymphosarcoma, the manner of spread in Hodgkin’s disease presents the problem whether the condition is multifocal in origin or whether metastasis occurs. It is thought that both methods exist.

Hodgkin’s disease becomes widespread and at post-mortem examination most organs in the body, including the skin and the skeleton, have been found to be involved.

Progress of the disease. In many cases of Hodgkin’s disease increasing fibrosis of the affected tissue takes place; in others, replacement of normal tissue by proliferating cellular masses occurs.

In a few cases a change in the rate of progress of the disease is observed tending to an increased degree of malignancy, whilst simultaneously a change in histological appearance of the lymph nodes and other tissues takes place (Fig. 10).

Reticular Lymphoma

This condition has been recognized recently. Some of the cases which have been called ‘early Hodgkin’s’ and ‘Hodgkin-like’ probably belong to this group. Jackson and Parker (1947) have suggested the name Hodgkin’s paragranuloma, and Robb-Smith (1947) has called it ‘lympho-reticular medullary reticulo-sis.’

Incidence. Reticular lymphoma is a rare condition accounting for only 5.1 per cent. of the group of cases at Westminster Hospital. No other series can be quoted from the literature, though Robb-Smith (1947) states that lympho-reticular medullary reticulosis has an incidence of 6.0 per million of population, and Bodley Scott (1948) states that for every six cases of Hodgkin’s disease, one case of lympho-reticular medullary reticulosis is found.

Age, sex and site incidence. Age and sex incidence are similar to those in Hodgkin’s disease. The disease presents with enlarged lymph nodes but does not seem to affect other tissues in the early stages. Any group of glands may be involved. At first the disease is localized to one group of lymph nodes, with little or no disturbance of the general health. It is slowly progressive and may remain latent for years following diagnosis. Jackson and Parker record a patient who has remained clinically well for 39 years since
the diagnosis was established although subsequent biopsies have shown the condition still to be present. A case at Westminster Hospital has been under observation for 15 years, but a recent biopsy of an enlarged cervical gland showed anaplastic changes.

Malignant changes may occur as the disease progresses. Robb-Smith says that 'Sarcomatous transformation may take place after an interval of 10 to 15 years.' However, in an example, from the series at Westminster Hospital, death from multiple metastases occurred five years after diagnosis.

Such a rapid course is probably exceptional as the other cases in this series have survived seven years or longer.

Pathology. The affected glands are enlarged but not to a very great size, so that the nodes examined in this series have measured 2 to 3 cm. in their longest diameter. They tend to remain discrete and are rubbery in consistency, of much the same type as Hodgkin's disease, being firmer than the glands of lympho-sarcoma. On cut surface they are greyish in colour and show no tendency to necrosis or haemorrhagic degeneration.

Microscopically the normal architecture of the lymph node is replaced by a proliferation almost entirely composed of mature lymphocytes, among which are scattered occasional reticulum cells. One of the characteristic features is that the reticulum cells remain isolated and do not tend to occupy clumps (Figs. 11, 12, 13). The reticulum cells, although relatively few in number as compared with Hodgkin's disease, are a clearly recognizable feature of the histological pattern and are easily identified at low magnifications. They possess the characteristic features of large well-defined nucleoli with prominent eosinophilic nucleolus and irregular pale eosinophilic cytoplasm. Binucleate forms have been seen but multinucleate 'giant' cells are not common. Mitoses have not been observed. Occasional eosinophils and plasma cells have been seen but are not a characteristic feature of the cytolgy. There is no tendency for capsule invasion or necrosis to occur. In the cases examined in this series, fibrous capsular thickening has been a frequent occurrence and collagen strands passing through the structure of the node have caused irregular lobulation frequently recognizable by the naked eye or hand lens examination of the sections. Particular attention has been paid to this feature in an account by Harrison (1952) (Fig. 11).

When more malignant changes supervene an increase in the number of proliferating reticulum cells is seen, so that the histological picture comes more to resemble a typical Hodgkin's disease of in the final stages, an anaplastic sarcoma of lymphoid tissue.

Harrison has suggested that if the condition ultimately assumes malignant form there is little...
FIG. 12.—Lymphocytes and scattered reticular cells in reticular lymphoma (H. & E. × 110).

FIG. 13.—Lymphocytes and scattered reticular cells in reticular lymphoma (H. & E. × 280).
value in making the diagnosis, but in his series of cases no malignant change had supervened. One cannot entirely agree with this concept, for it seems reasonable to identify a condition by name which is likely to pursue a favourable course, even if it is realized that after a period of time advancing malignancy may supervene.

The name for this condition gives rise to some difficulty. Jackson and Parker have used the term 'Hodgkin's paragranuloma' as they consider that it bears a close resemblance to Hodgkin's disease, which they term 'Hodgkin's granuloma' and that the condition is of inflammatory origin and that it is not improbable that the paragranulomatous form bears to the granulomatous type of the disease the same relation that a primary tubercle does to fibro-caseous tuberculosis.'

It is thought that this idea is essentially incorrect and that the disease provides another example of a tumour which may remain benign for a long period yet at all times is potentially malignant. Robb-Smith's title 'lympho-recticular medullary reticulosis' is suitable as it describes the cell types found in the tumour. However, the name is cumbersome and it is felt that the concept of a medullary reticulosis, as has already been indicated, is an artificial sub-division. The term 'recticular lymphoma' fits better into the general scheme of terminology and at the same time indicates the cellular constituents of the tumour.

Reticulum Cell Sarcoma

Under this heading are included tumours of the lymphoid tissue where the cellular elements show a gross predominance of reticulum cells.

From a review of the literature it seems that the term 'reticulum cell sarcoma' or 'reticulosarcoma' is usually applied to cases with pleomorphic appearance and a bad prognosis which are here included in the anaplastic group. Different authors apply a variety of meanings to the name and this causes great confusion.

An attempt has been made, therefore, to include under this heading only those cases which show a genuine preponderance of reticulum cells.

As it is believed that reticulum cells produce the argyrophil network on which collagen is laid down, the better differentiated tumours of this group can be expected to show fibrosis. Thus great difficulty may be experienced in differentiating these cases from the sclerotic form of Hodgkin's disease.

The majority of these sclerotic varieties can be grouped with Hodgkin's disease and seem to have a similar prognosis. Occasionally tumours are seen where intense cellular activity of reticulum cell type is found although considerable fibrosis has taken place. Such tumours are extremely rare.

Another difficulty experienced in diagnosing reticulum cell sarcoma is in differentiating metstatic carcinoma, a condition which must constantly be borne in mind whenever the histological diagnosis of malignancy in lymphatic tissue presents difficulty.

Age, sex and site incidence. Of the 410 tumours of lymphatic tissue from the Westminster Hospital series, 21 cases seem to justify the title reticular cell sarcoma. The presenting sign in most of these cases was a swelling in the neck. Despite its rarity the condition seems to be a definite clinical and pathological entity.

Pathology. Organs affected by reticulum cell sarcoma show no macroscopic features which can be used to distinguish them from other primary tumours of lymphoid tissue. Tumour material is whitish in colour and the majority is rubbery in consistency. Areas of fibrosis may occur as my zones of softening due to necrosis.

The histological picture consists of a replacement of normal architecture by sheets of large cells varying from 12 μ, to 20 μ in diameter, with large well-defined nuclei frequently containing one or more somewhat eosinophilic nucleoli (Fig. 14). The cytoplasm is irregular in quantity and outline and stains palely with eosin. Silver impregnated sections show reticulin fibres scattered diffusely among the cells and sometimes interlacing prolongations join one cell with its neighbour. Giant multinucleate forms may occur but are not very common. Mitoses are seen but are not very frequent. Areas of necrosis and fibrosis are scattered irregularly throughout the cellular mass and fibrosis may be of considerable degree.

Anaplastic Sarcoma of Lymphoid Tissue

Under this heading are included all those tumours of rapidly advancing malignant nature and anaplastic histological structure which have been indicated as occurring at the apex of the triangle in Table 1.

Incidence. Classifying the anaplastic tumours in the above manner 70 such cases were thus sub-divided in the series from Westminster Hospital.

Age, sex and site incidence. These tumours spread rapidly throughout the body and primary sites are very variable, although cervical, mediastinal and abdominal masses are perhaps more frequent than others.

Metastases are found scattered throughout all organs and a feature at autopsy is the widespread nature of the disease. No sex predominance has been noticeable in our cases. The older age groups have been more commonly affected although cases occur at all ages.

Morbid anatomy and histology. Soft whitish non-encapsulated masses showing a marked tendency...
FIG. 14.—Diffuse sheet of reticular cells in reticular cell sarcoma (H. & E. × 450).

FIG. 15.—Anaplastic cellular proliferation from a case of anaplastic sarcoma and lymphoid tissue (H. & E. × 450.)
to necrosis and haemorrhagic degeneration are the feature of this group of disease.

The histological picture is one of pleomorphic cell proliferation showing anaplasia and rapid growth as demonstrated by numerous normal and abnormal mitotic figures. Great variability of histological appearance is seen. Not only may the pattern and cytology differ from one mass to another in the same patient, but widely dissimilar pictures may be observed in different parts of the same tumour (Fig. 15, see also Fig. 10).

Many authors have described different varieties of these anaplastic tumours under such titles as ‘lymphoblastic reticulosarcoma,’ ‘syncytial reticulum cell sarcoma’ and ‘Hodgkin's sarcoma’ thus indicating a proliferation of the precursors of lymphocytes, reticulum cells or a mixture of cells respectively. Whilst it is agreed that in some tumours and certainly in some areas of tumours such cytological specificity can be made out, the variation is so great that in the majority of cases no such clear-cut differentiation can be demonstrated. No sub-division of the anaplastic group of tumours seems possible (Willis, 1948).

Conclusion

In grouping tumours of lymphoid tissue it is useful to stress the manner in which patients present, in order to realize the exact nature of the diagnostic problem.

Excluding general symptoms such as tiredness, and viewing the position from a morbid anatomical standpoint, it may be said that the vast majority of patients complain of the presence of a "lump" which as often as not is found to be an enlarged lymph node mass belonging to one of the superficial groups. Frequently on examination other enlarged lymph nodes are discovered with or without the presence of splenomegaly. More rarely abdominal masses or signs of respiratory or vascular obstruction resultant upon a mediastinal tumour provide the initial features.

One may generalize, therefore, by saying that although clinical study of the type of tumour taken in association with age and sex may be of value, the final diagnosis is usually dependent upon study of tissue obtained at biopsy.

Clearly, therefore, it is important to recognize the differential diagnostic possibilities before labelling a primary tumour arising in lymphoid tissue. It is not the purpose here to make a detailed examination of the differential diagnosis for this has been dealt with fully elsewhere (Lumb, 1954), but it may be briefly divided into:

1. Inflammatory conditions which may be sub-acute or chronic.

2. Metastases from malignant disease elsewhere—usually carcinoma.

It is of the utmost importance constantly to bear these features in mind otherwise such well-known difficulties of diagnosis as glandular fever or brucellosis in the inflammatory group will pass unnoticed, whilst the danger of mistaking metastatic carcinoma for a primary tumour of lymphatic tissue is obvious. Indeed one may now modify the statement made above as regards diagnosis by biopsy in stating that only by a close correlation of clinical features and blood picture with histological appearances can a diagnosis be made.

Once it has been decided that a primary lymphatic tissue tumour is present it seems true to say that the vast majority of cases will fall into one of the following common groups:

2. Lymphosarcoma.
3. The anaplastic sarcoma group.

Of the remainder, those in the follicular lymphoma group are easy to distinguish microscopically and there is a left a small number of cases which may be diagnosed as reticular lymphoma, reticulum cell sarcoma or may defy dogmatic histological diagnosis. This latter group, where diagnosis is not made, may further be sub-divided as follows:

1. Those where a confident diagnosis of lymphatic tissue tumour can be made but where it is difficult to apply a specific name. These cases are very rare and it is thought better to describe them in terms of their cellular differentiation as a guide to prognosis rather than to invent numerous different names for them. In other words such tumours may be said to fall somewhere within the triangle indicated in Table 1 as opposed to being on one of the focal points of the triangle.

2. Those where it is not certain whether the disease is a primary tumour or whether it is a metastasis.

3. Those where inflammatory conditions cannot be excluded histologically.

It is considered of value to present the picture of routine diagnosis in the above manner as it serves to place the rarer conditions where diagnosis is difficult in their proper perspective and to indicate that even where no specific name can be applied to a condition it may be possible to elicit general indications relating to prognosis.

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