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If this somewhat sketchy paper raises the interest of a group of student workers to obtain facts and figures for a more exact statistical survey than I was able to produce, it will achieve more than the great personal value that the work has been for me.

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The Lymphomata*

A Suggested New Classification and General Clinical Features

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A lymphoma is defined as a primary neoplasm arising in lymphoid tissue. This lymphoid tissue has a definite histological picture, and besides being aggregated to form lymph glands, is found in the form of microscopic nodules in every organ in the body except the brain and spinal cord. The lymphoid tissue contains many varieties of cell and from each of these a neoplasm may arise. Because of the intimate relationships of these cells, the histological picture is often extremely varied and impossible to classify except to the highly skilled pathologist.

The lymph gland or lymph node may be considered to be made up of three tissues; the follicles, medullary cords and the sinuses. These actually correspond to the cell types in the gland. The follicles are largely made up of lymphocytes, and their precursors the lymphoblasts, the medullary cords of reticular cells and the sinuses of littoral cells. As these cells are the parent cells of the various lymphomata it would be well to examine them more closely.

The Lymphocytes.

These are the small cells found circulating in the blood stream. In the lymphoid tissue these cells loosely impregnate the whole gland but are most concentrated at the periphery of the follicles.

The Lymphoblasts.

These are larger cells than the lymphocytes and are not normally found circulating in the peripheral blood stream. They are the direct precursors of the lymphocytes and form the germinal centre of the follicle.

Reticular Cells.

These cells are part of the Reticulo-Endothelial system and are intimately associated with the argyrophil reticular fibres found in lymphoid tissue. In the lymph nodes they form the matrix of the medullary cords and are lightly impregnated with lymphocytes. The follicles also contain not inconsiderable numbers of reticular cells which are often confused histologically with lymphoblasts which they may resemble very closely. They are small inconspicuous stellate cells, but under pathological stress they become free amoeboid cells (Histiocytes, Epithelioid cells, Macrophages) that are so conspicuous a feature of chronic inflammatory processes. Sabin's view which is the most acceptable is that these cells are the precursors of the lymphoid cells (lymphoblasts, lymphocytes), the myeloid cells (myeloblasts, myelocytes and polymorphs) and the monocyte series. The monocytes formed from this cell form the majority of large mononuclear cells in the blood stream.

Littoral Cells.

These cells are also part of the Reticulo-Endothelial system and are found lining the

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sinusoids of the lymph nodes (subcapsular and medullary), the sinusoids of the spleen, bone marrow, liver (Kupffer cells), pituitary and adrenal. They are sometimes known as Endothelial cells, but as they are different from the endothelial cells of the blood vessels, they have been called Littoral cells (Latin: litus or littus —a shore). These cells also give rise to the macrophages or Histiocytes found in chronic inflammation and the large mononuclear cells in the blood stream which are very similar to the ordinary monocyte but can be distinguished by special methods. The cells are sometimes known as Clasmatocytes.

Having recognised the cells present in the normal lymph node we may then proceed to classify the lymphomata as follows:—

(A) Arising from lymphocytes and their precursors.

(i) From lymphoblasts — Lymphoblastic lymphoma.

(ii) From lymphocytes — Lymphocytic lymphoma.

(iii) From mature follicles — Follicular lymphoma.

(B) Arising from Reticular Cells.

(C) Arising from Littoral Cells.

This classification has the virtue of simplicity and agrees as closely as possible with what we know of the cells present in the normal lymph node.

It should be mentioned that a benign lymphoma, i.e., a primary benign tumor of lymph nodes, has not been satisfactorily demonstrated, and the tumors to be discussed are all malignant.

(A) Arising from Lymphocytes and their precursors.

(i) Lymphoblastic lymphoma.

This neoplasm, as the name implies, arises from lymphoblasts. According to some it may be classified further into diffuse and focal growths. The diffuse growth is what we, up to the present, have called acute lymphatic (lymphoid, lymphocytic, lymphogenous) leukaemia. The focal growth is one of the varieties of lymphosarcoma often known as lymphoblastoma or small round-celled sarcoma of a lymph gland. Microscopically no difference can be recognised between the diffuse and focal growth, all stages of diffuse involvements are seen and the presence of abnormal cells in the circulation (leukaemia) may or may not be a feature of either. The combination of a focal growth (lymphosarcoma) and abnormal circulating cells is known as a leukosarcoma.

(ii) Lymphocytic lymphoma.

This neoplasm arises from mature lymphocytes. Again it may be subclassified into diffuse and focal growths. The diffuse growth is what is known as chronic lymphatic (lymphoid, lymphocytic, lymphogenous) leukaemia, the focal growth as lymphocytoma, one type of lymphosarcoma or of small round-celled sarcoma. The picture is in all respects identical with the lymphoblastic lymphoma except that the type cell is the mature lymphocyte.

(iii) Follicular lymphoma.

This condition has only recently been recognised: It was first described by Brill, Baehr, and Rosenthal in 1925 and soon after by Symmers. At first thought to be benign, the neoplasm is now recognised to have a low grade of malignancy. Pathologically there is enormous enlargement of the follicles which still retain some semblance of the structure of normal follicles. This is the criterion for recognising it pathologically. It is actually an orderly but enormous neoplasia of the mature lymphocytes, still existing in follicles. These enlarged follicles are found wherever lymphoid tissue is found. The condition is sometimes known as Brill-Symmers’ disease. A certain small proportion (about 2—3%) of the described cases have been reported to have a leukaemia blood picture.

(B) Arising from Reticular Cells.

These neoplasms are a vaguely defined group and are usually associated with the excessive production of reticular fibres. They are all extremely rare with the exception of Hodgkin’s disease. There are several conditions under this heading which form the bulk of what are known as Reticulo-Endothelioses and they may be subdivided as before into diffuse and focal growths. It is not improbable that further work will demonstrate, as with the lymphoid series, the essential unity of this whole group.

The generalised growths include:—

(1) Hodgkin’s disease (lymphadenoma) and Hodgkin’s sarcoma.

(2) Monocytic leukaemia. Most cases described fall under the reticular proliferations. The remainder fit into a group to be described later.

(3) Aleukaemic Reticulo-Endotheliosis. Microscopically this is similar to the above but the leukaemic blood picture is absent.

(4) Certain very rare conditions of Reticular cell overgrowth, the least known of which are the Letterer-Siwe syndrome (an acute Reticulo-Endotheliosis of
childhood) and probably Boeck's Sarcoïd.

These conditions are all characterised by a diffuse overgrowth of the reticular cells, often with excessive reticular fibre production. The focal group is similar microscopically, but at the beginning the growth is confined to one node or group of nodes. It includes:

(1) One variety of Reticulum cell sarcoma (Stem cell lymphoma—Mallory and Gall, Retothelial sarcoma—Roulet, large-celled lymphosarcoma).

(2) Malignant monoblastoma. This growth is said to be composed of monoblasts. In all probability it is identical with the Reticulum cell sarcoma.

(C) From Littoral Cells.

This is an even more badly defined and ill-understood group than the Reticular cell proliferations, and includes the remainder of the Reticulo-Endotheliose. As with the Reticular cell proliferations it is more than probable that this whole group is one single condition. It can as before be subdivided into diffuse and focal proliferations.

The diffuse type includes:

(1) Clasmatocytic Leukaemia. This is usually not recognised as such but is labelled Monocytic Leukaemia, from which it can only be differentiated by supra-vital staining. Pathologically there is an overgrowth of the Littoral (Endothelial) cells and the appearance of abnormal mononuclears (Clasmatocytes) in the blood stream. No aleukaeemic variety has yet been reported but undoubtedly a few cases will eventually appear in the literature.

(2) An extremely rare condition described by Stengel and Wolbach in 1911 of diffuse Littoral Cell overgrowth (Stengel-Wolbach Sclerosis).

The focal group of neoplasms includes only:

(1) One variety of Reticulum-cell sarcoma (Endothelioma of lymph gland—Ewing, large-celled lymphosarcoma). This is usually distinguished from the type arising from the Reticular cell by the absence of excessive formation of Reticulum fibres.

This classification and description covers almost all the known neoplasias and hyperplasias in lymph glands. It must not be forgotten that owing to the ubiquitous presence of lymphoid tissue the condition may first manifest itself in almost any organ and earn for itself the title of a special syndrome or disease, i.e., in the skin—Mycosis fungoides; in the ciliary tract of the eye and in the salivary glands, uveo-parotid fever, and in the salivary and lachrymal glands, Mikulicz's disease. Many malignant bone tumours are probably lymphomata and many people consider Ewing's tumour to be a Littoral cell tumour of the marrow. The Lipoidoses, i.e., Gaucher's and Niemann-Pick's disease, etc., have not been discussed because it is believed that they are not true neoplasms.

Clinical Features.

The lymphoma may manifest themselves in a multitude of ways. There is no definite clinical picture attributable to any one or all of these conditions. The picture to be described may occur in any of the lymphomata; differential clinical features are merely suggestive but never pathognomonic.

Etiology.

They are believed to be neoplastic in nature. In spite of the fact that 10% of the lymphomata are associated with tuberculosis, no causal relationship has been proved.

Clinical Picture.

Age: Commonest between 36 and 50 years but may occur at any age.

Sex: Males predominate over females in the ratio of 2:1.

General Symptoms: Weakness, malaise, loss of appetite and of ability to concentrate are common early findings.

Glandular Enlargement is the most common feature of all the lymphomata, 90% having visible or palpable glands.

Splenomegaly is found in about half the cases.

Fever is found in about half the cases, every variety having been encountered. The Pel-Ebstein phenomenon is uncommon, being found in 16% of cases.

Cachexia is rare in the early stages but common terminally.

Compression Symptoms may occur in practically any viscus, e.g., Intestinal or Bronchial Obstruction.

Skin Infiltrations produce a bewildering variety of pictures from scattered nodules to diffuse infiltrations; pruritus is found in about 20% of cases.

Ulcration of the Mouth is found in about one quarter of the cases.

Priapism, although quoted as occurring commonly, is found only very occasionally.

Cough and Pain in the Chest occurs in about 15% of cases.
Bone Lesions occur uncommonly.
Pathological fractures and joint pains resembling rheumatic fever have been recorded.

Eye Symptoms: Retinal haemorrhages, retinitis and corneal ulcers have been described.

Central Nervous System. In about one quarter of the cases neurological signs are found. Cerebral haemorrhages, meningeal infiltrations and cranial nerve lesions are the commonest findings. The cerebro-spinal fluid usually shows an increased pressure, pleocytosis and increased protein.

Blood Picture: This is extremely important but very inconstant. Anaemia of about 3½ million red cells is almost invariable. The white cells show marked variation in number, leucopenia or leukaemia being often noted. Eosinophilia, though to be so common in Hodgkin's disease, occurs in about 5% of cases. Thrombocytosis, or more commonly thrombocytopenia with purpuric manifestations, is a common finding. The appearance of abnormal cells in the circulation (leukaemia) occurs in under 40% of all the lymphomas. It may occur in any of the lymphomas, the abnormal cells usually being the type cell of the neoplasm. The B.M.R. is commonly raised.

The only method of establishing an accurate diagnosis is by biopsy of a gland, and microscopic examination by a skilled pathologist.

Differential Diagnosis.
The most important conditions resembling the lymphomas are:—
(1) Tuberculous lymphadenitis.
(2) Infectious Mononucleosis.
(3) Generalised carcinomatosis.
(4) The lipoidoses.
(5) Infections, e.g. Brucellosis, Typhoid and Whooping Cough.

Prognosis,
With or without treatment the condition progresses to its inevitable termination in about 2-4 years. Treatment does not halt the progress of the condition but merely alleviates the symptoms.

Treatment.
There is no satisfactory treatment.
(1) X-rays are useful in the more chronic types, but harmful in the acute.
(2) Surgery is indicated in strictly localised lesions and cases of complete cure have been reported, although extremely uncommon.
Splenectomy should never be performed.
(3) Radio-active phosphorus ($^{32}P$) is the newest form of treatment. It has been proved at least equal to radio-therapy.

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This war, the item (b) at least, is very likely to be greatly exceeded.

There is very little news from the occupied areas of Russia, but it must be borne in mind that the scorched-earth policy which was followed by Russia is a two-edged sword—that while it slows up the advance of the invading army it also makes the prospects of the population left behind almost hopeless. The sufferings of the Russian nation in respect of soldiers dying in battle and prisoners-of-war dying in prisoner camps has dwarfed, by comparison, anything that any other ally has been subjected to, but the sufferings of the civilian populations in the occupied territories are likely, when the whole grim story is told, to exceed even these.