LYMPHOMAS AND LEUKEMIAS
Pathological and Histogenetic Aspects

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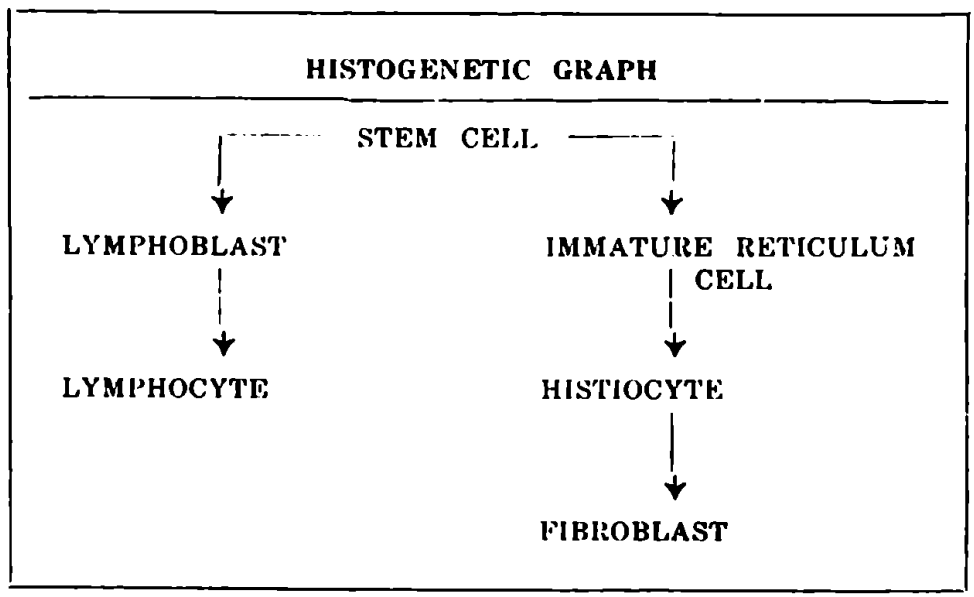
Lymphomas and leukemias are both malignant neoplasms of the hematopoietic system. Lymphomas form a group of malignant tumors arising usually in multiple foci, from the lymphoid-reticular system. As every organ in the body normally has lymphoid and reticular cell components, each can be a primary site for these tumors. The different organs are affected roughly in the following frequencies: lymph nodes are involved in 90 per cent of cases; spleen, 50 per cent; bone marrow, 20 per cent; other viscera as the liver, lungs, kidneys, and gastrointestinal tract, 10 per cent; and central nervous system, 0.5 to 1 per cent. Lymphomas may start as a solitary lesion and may remain as such for a long time. As a rule, however, the lesions are multiple from the beginning. The multiplicity of lesions is due to the systematic nature of the disease and usually not to metastases. Occasionally, however, dissemination by metastases may occur.

Lymphomas are composed primarily of immature and/or mature cells of the lymphoid-reticular system. For a clearer concept of the origin of cells forming the lymphomas, let us review the histogenetic graph below:



It is widely accepted that lymphoid and reticular cells arise from a common cell — the lymphoid-reticular cell. Lymphomas may arise from these cells at any stage in their development. The type of lymphoma depends on the degree of immaturity of the cells and on the direction of differentiation. If the tumor cells arise from the stem cell stage, a stem-cell lymphoma develops; if from the lymphoblast, lymphoblastic lymphosarcoma results; if from the lymphocyte, lymphocytic lymphosarcoma; if from the immature reticulum cell, reticulum cell sarcoma, if from the histiocytic stage, clasmatocytic type of reticulum-cell sarcoma. Where then is the origin of Hodgkin's disease? For a diagnosis of Hodgkin's disease, the Dorothy-Reed Sternberg cell must be present. This polymorphous giant cell is but an atypical form of the reticulum cell — a peculiar reaction to the unknown etiologic agent of Hodgkin's disease. Aside from this pathognomonic cell in Hodgkin's disease, there is much histologic pleomorphism in this type, especially in Hodgkin's granuloma.

Based on the histology, lymphomas are placed under two main groups:

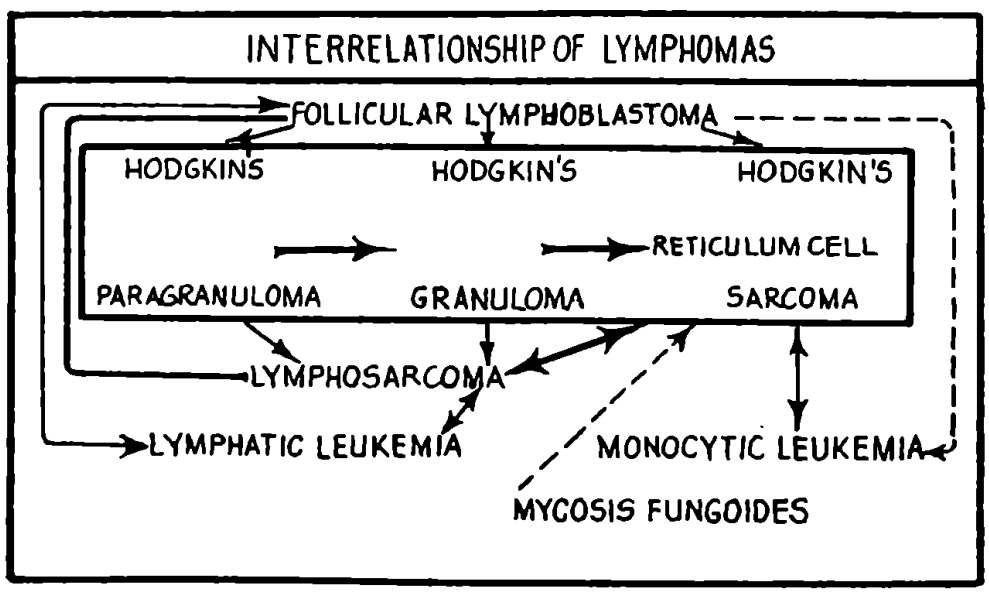
I. Monomorphous
   1. Stem-cell lymphoma
   2. Reticulum cell lymphoma
   3. Lymphoblastic lymphoma
   4. Lymphocytic lymphoma
   5. Giant follicular lymphoma.

II. Polymorphous
   6. Hodgkin's disease
   7. Mycosis fungoides

The monomorphous group includes all the types which are composed wholly of tumor cells. Polymorphous group includes the types which have inflammatory elements aside from the tumor cells. These inflammatory elements may include inflammatory cells of neutrophils, eosinophils, plasma cells, histiocytes, and fibroblasts, at times to the extent of large areas of fibrosis. It is believed that these inflammatory cells and fibrosis repre-

sent a favorable reaction on the part of the host to the disease. In Hodgkin's paragranuloma, the inflammatory elements, except for a few, scattered, isolated Reed-Sternberg cells may chiefly comprise the tumor. The relationship of Hodgkin's paragranuloma to Hodgkin's granuloma may be analogous to the relationship of a primary tubercle to a fibrocaseous type of tuberculosis. Hodgkin's sarcoma is reticulum cell sarcoma plus Reed-Sternberg cells. Mycosis fungoides, a malignant lymphoma of the skin has also a polymorphous picture, similar to Hodgkin's granuloma.

It has been observed by many that cases of malignant lymphoma sometimes present features of more than one variety or exhibit changes in type during the course of the disease. Actually, this has also been the observation in the U.P.-P.G.H. Medical Center based on autopsies and/or biopsies of patients with malignant lymphomas. The following is a graph based on the study of Custer and Bernhard on 1,300 cases of malignant lymphomas in the Armed Forces Institute of Pathology, Washington, D.C. This study based on biopsy and later autopsy or on sequential biopsies of the same case gives further evidence of the above observation.



The heavy lines indicate the most frequent transitions; the lighter lines, the less frequent; and the dotted lines, the unusual transitions actually observed. Only about 20 per cent maintain a pure type lesion throughout their course. Fifty-five per cent show 2 or more types of lesion. Approximately 40 per cent of autopsied cases having previous biopsy display a complete alteration of histologic pattern from one type to another. Follicular lymphoblastoma or giant follicular lymphoma may follow a benign clinical course for years, the longest being 17 years. At this stage, it should be differentiated from reactive hyperplasia of the lymph node. Hodgkin's paragranuloma may have the same benign clinical course for years as follicular lymphoblastoma, but with the passage of time one type undergoes transition into other types. In general, cases tended to progress towards greater malignancy, though this is not invariable. These observations are of great interest because they indicate an underlying unity in these groups of diseases. They are also a warning against any too rigid system of classification based on purely histologic criteria. Nevertheless, in spite of these transitions, it is essential for the understanding of the clinical features to recognize the existence of each type.

Abnormal reticulum cells in monocytic leukemia are sometimes indistinguishable from Sternberg-Reed cells. Repeated observations of this phenomenon have led to the conclusion that Hodgkin's sarcoma and reticulum cell sarcoma are identical and are closely allied to monocytic leukemia.

At either end of the scale lymphosarcoma and lymphatic leukemia are distinct clinical entities, but there is a very large number of cases in which a clear distinction is not possible. The mere presence of abnormal lymphoid cells in the circulating blood is not adequate definition because a considerable number of cases show characteristics of lymphosarcoma for a long time before developing a leukemia blood picture. Equally, the presence of tissue invasion does not exclude a leukemia blood picture. Histologically, neither the pattern of tissue nor the cell cytology assists in making a distinction though the presence of leukemic blood can be recognized in tissue sections. It is only by taking into consideration everything — the clinical history, complete blood and bone marrow examinations, repeatedly done during the course of the illness, and biopsy of different

organs as lymph node, spleen, or liver that a definite diagnosis can be given. At present, one can say that although two typical disease entities can be defined, the overlap is sufficient to suggest that they may well prove to be variants of one basic process. Dr. Khokhlova of the Pathologo-anatomical Laboratory in Lenin Institute of Hematology and Blood Transfusion conducted a series of experiments, wherein he injected benzol extracts of organs from leukemic patients into mice. He brought about the following results in the mice: leukemia alone, leukemia and tumor formation, or tumor alone. This again is an observation suggesting a close pathogenetic relationship between the two diseases. There seems to be a permeable boundary line between lymphomas and leukemias. In the former, there may be a release of immature tumor cells into the blood stream; on the other hand, a true leukemia may present features of lymphoma when actual tumor formations are formed in the different organs.

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