THE GENETIC NEOPLASTIC RELATIONSHIPS OF HODGKIN'S DISEASE, ALEUKÆMIC AND LEUKÆMIC LYMPHOBLASTOMA, AND MYCOSIS FUNGOIDES

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In 100,000 diagnostic tissue examinations made in the Pathological Laboratory of the University of Michigan between the years 1895 and 1927 there were 506 cases, approximately 0.5+ per cent. of all cases, diagnosed as Hodgkin's disease, aleukæmic and leukæmic lymphoblastoma, and mycosis fungoides. These cases were further distributed, as to diagnosis, as follows:

Hodgkin's	
Typical Hodgkin's	94
Atypical Hodgkin's	83
Sarcomatous Hodgkin's	29
Leukæmic Hodgkin's, lymphatic	6
Leukæmic Hodgkin's, myelæmic	2
Hodgkin's becoming lymphosarcoma	12
Abdominal Hodgkin's	3
Hepatic Hodgkin's, cirrhosis	2
Cutaneous Hodgkin's, mycosis	1
(Non-caseating tuberculosis with clinical diagnosis of Hodgkin's	10)
Lymphoblastoma (lymphosarcoma)	
Typical glandular lymphoblastoma	134
Typical abdominal lymphoblastoma, gastro-intestinal, *etc.*	26
Typical tonsillar lymphoblastoma	19
Typical aleukæmic lymphoblastoma becoming leukæmic	9
Atypical glandular lymphoblastoma	44
Mycosis fungoides	
Aleukæmic lymphoblastoma	23
Aleukæmic lymphoblastoma becoming leukæmic	5
Aleukæmic myeloblastoma	1
Leukæmia cutis	3

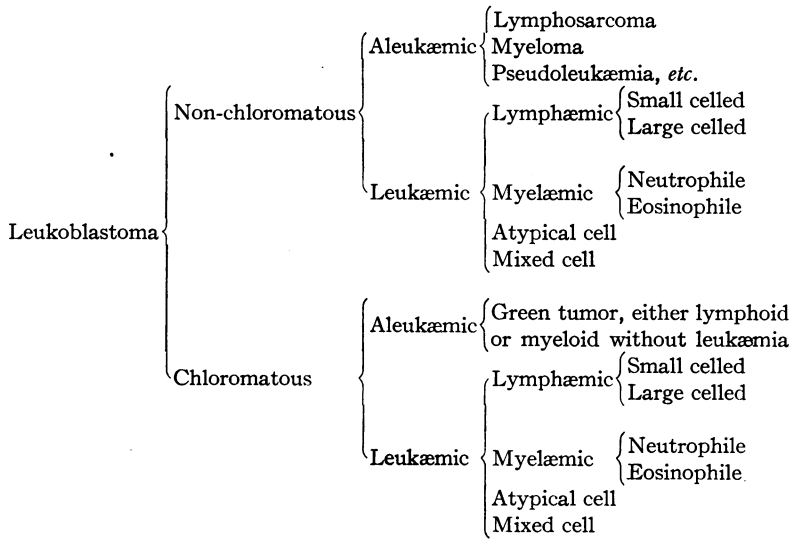
During the same period, in 2,000 autopsies there were 83 (4.1 per cent.) cases falling into the same diagnostic categories, as follows:

Myelæmic leukæmia	24
Leukæmic lymphoblastoma	20
Aleukæmic lymphoblastoma	20
Hodgkin's, typical	7
Aleukæmic mycosis fungoides	5
Leukæmic mycosis fungoides	3
Hodgkin's mycosis fungoides	1
Plasma-celled mycosis fungoides	1
Myeloid mycosis fungoides	1
Eosinophile (myeloctye) mycosis fungoides	1

The study of this material, as outlined above, has formed the basis for the writer's belief that Hodgkin's disease is a neoplasm and related genetically to the lymphoblastomas, of which both the aleukæmic and the leukæmic forms are identical pathologically; and that mycosis fungoides is likewise a neoplasm belonging to the same generic group. The essential differences between these different clinical forms consist in different degrees of differentiation or entdifferentiation, and the organ or tissue primarily involved. Transition forms exist between all of these groups, and one type may be transformed into another. Clinically they all possess the characters of malignancy; no cure is known for any one of them; they progress inevitably to a fatal termination, sometimes rapidly, sometimes very slowly. They all show infiltrative tendencies and metastasize, ultimately involving all of the reticulo-endothelial and blood-cell forming tissues of the body. They show an abundance of mitotic cell-division figures, both typical and atypical, as well as amitotic cell division. Their growth is at times rapid, at other times slow; they are characterized by their marked tendency to degenerations and necrosis. Marked fibrosis often follows the degenerative changes. At times the regressive tendencies are so marked that so great a reduction in size of the growths takes place, that clinically they may become so greatly diminished in size as apparently to disappear. A certain degree of fever frequently accompanies such periods of marked retrogression. Periods of the aleukæmic state may alternate with leukæmic periods. The acute transformation into a leukæmia is sometimes preagonal. The general effects upon the patient are in every way comparable to those of tumor cachexia; progressive anæmia, emaciation, weakness and exhaustion. Although regarded many times as representing infectious processes, no organism described as a possible etiologic factor has ever met the test; moreover, the clinical and pathologic pictures presented are those of a progressive fatal malignancy. No mild cases exist; no cures have ever been observed for any one of the forms belonging to this group. There is no evidence of any immunity process; no specific antibodies are found in the serum. In all of these forms the pathologic picture is that of a progressive increase of atypical tissue replacing the normal tissues of the body, up to a point at which life is no longer possible, or secondary complications may end the picture.

More than twenty-five years ago the writer's study of chloroma convinced him that "Chloroma is a tumor-like hyperplasia of the parent-cells of the leucocytes, primary in the red marrow, the periosteum being involved only secondarily." This was new pathology at the time, but this view has been generally accepted since. In 1904 he observed an aleukæmic lymphosarcoma (lymphoblastoma), primary in the intestine, become transformed into the leukæmic stage after a surgical operation for removal of the appendix. This case was reported in the *Transactions* of the Association of American Physicians, in 1904, under the title of "The Neoplasm Theory of Leukemia, with Report of a Case Supporting This View." It was regarded by the writer as presenting the same evidence of malignant neoplasm nature, in its infiltrations and metastases, as did the chloroma case, and in this article he

made the statement that "leukemia must be regarded as a neoplastic hyperplasia of the parent cells of the blood cells." For this neoplasm, he suggested the term *leukoblastoma,* and offered the following classification of the leukæmic and aleukæmic neoplasms:



This was at a time when no textbook considered the possibility of the neoplastic nature of leukæmia, but a certainty of conviction as to the correctness of this view has remained in the writer's mind ever since, and he has had in recent years the satisfaction of seeing an increasing acceptance of this view. In spite of the prevailing universal belief that Hodgkin's disease was an infective granuloma, he very early was led to include this disease in the same group with the aleukæmic and leukæmic lymphosarcomas, because of observed cases showing such transitions from typical Hodgkin's into the other forms. His experience was the same as far as mycosis fungoides was concerned, and this clinical form he brought also into the same group of generic relationship. While the limits of this paper are too brief to enter into any detailed description of epoch-making cases observed, or into extended arguments over the relationship of the different forms, an attempt will be made to give a concise and succinct statement of the writer's views on this question, and the chief reasons in support of these views.

Hodgkin's Disease.—Typical Hodgkin's presents a characteristic and easily recognizable histological picture. The most marked feature is at first a localized or focal proliferation of the reticulum with the presence of atypical lymphocytes, lymphoblasts, plasma cells, mononuclear and polynuclear eosinophiles, myeloid cells, fibroblastic cells, and the multinucleated "Hodgkin's" or "Dorothy Reed" giant cell, which resembles those of the bone-marrow. These and the eosinophile cells constitute the chief diagnostic factors microscopically; and our diagnoses of typical Hodgkin's rests upon their presence and is never made in their absence. As the disease becomes more chronic these foci in these lymph-nodes become more fibrous, the struc-

ture of the node is wholly lost, and its appearance becomes that of a multicentric nodular mass, the active nodules separated from each other by dense fibrous connective tissue. In the more actively growing cellular forms degeneration and necrosis occur frequently; often these degenerative changes are so marked that a great reduction in their size, even to that of the normal node, may result. The disease may begin anywhere in the body where there is primitive lymphoid tissue or reticulo-endothelial tissue. In our experience the left cervical nodes have been most often the clinical point of origin; then the right cervical region; then the axillary, inguinal, mediastinal, and retroperitoneal nodes in the order named. The process may also be primary, or at least most marked, in the tonsil, thymus, bone-marrow, spleen, liver and skin. We have diagnosed Hodgkin's in the tonsil before any enlargement of the lymph-nodes was clinically apparent. Ultimately, all of the lymphoid tissue in the body is involved in the process, and throughout the reticulo-endothelial tissues of the peri-lymph-node adipose tissue, in the mediastinum, retroperitoneal adipose tissue, and subcutaneous fat, small nodules, or more diffuse infiltrations, showing the same histologic structure as the lymph-nodes develop. Even in the meninges Hodgkin's foci may be present. In old and advanced cases the liver may present the appearance of a Hodgkin's cirrhosis; even in the kidneys and testes metastatic nodules and infiltrations may be found. The lungs may also not infrequently show numerous typical Hodgkin's nodules and infiltrations. The heart usually escapes, but even in this organ we have found small Hodgkin's nodules, and in one case of mediastinal Hodgkin's (thymoma) the heart showed marked involvement. Further, in late Hodgkin's atypical cells are found in small masses in the splenic, kidney and liver capillaries, apparently free, or forming small emboli, proving beyond any doubt the occurrence of metastasis. When recognized clinically the disease is as a rule well advanced and the majority of the lymph-nodes show the typical lesion. As the lymph-nodes become progressively replaced by the atypical tissues, all normal lymph-node structure disappears, the sinuses are obliterated, the germ centres are lost, and the distinction between cortex and medulla can no longer be made out. Around the nodes so altered there is a progressive new formation of lymphoid tissue which in turn becomes involved in the process. After removal of diseased nodes there occurs a similar regeneration of nodes that ultimately show the characteristic changes of the disease. Not all cases of Hodgkin's show a febrile reaction, but in the majority there is an irregular fever curve, especially marked in the case of degenerating nodes. Secondary infection of the necrotic areas is undoubtedly responsible for the septic fever curves and night sweats found in some cases. The disease occurs most frequently in the young adult; our earliest case was in a child three years old, and the oldest in a male of seventy. It is relatively uncommon after the age of forty. The usual limit of life after relatively early diagnosis is three to five years. X-ray irradiation is the only treatment that will prolong life; in some cases under constant and experienced supervision the limit of life has been extended to seven, nine, ten and twelve years. In spite of repeated irradiation the disease process ultimately conquers, and in

these late cases there is an extraordinary extension of the lesions to practically all organs and tissues. In two of our X-ray cases there occurred a transformation of the pathological lesions into those of myelæmic leukæmia; in six other cases lymphatic leukæmia developed spontaneously without X-ray irradiation. There were three primary abdominal Hodgkin's in this series, involving particularly the spleen, a splenomegaly being the chief clinical feature; and the disease was diagnosed in this organ after splenectomy, which was followed by a gradual generalization of the process. In two cases the chief clinical symptoms were hepatic, and microscopic examination of the enormously enlarged livers showed typical Hodgkin's involvement of all the periportal tissues—a pathological picture justifying the use of the descriptive term, Hodgkin's cirrhosis. The spleen showed similar lesions in these cases, and Hodgkin's foci were found in the lymph-nodes and bone-marrow, but nowhere to the extent shown in the liver. Further, in one clinical case of mycosis fungoides the skin lesions were typically those of Hodgkin's. In ten cases diagnosed clinically as Hodgkin's, a diffuse miliary non-caseating tuberculosis was found in the excised nodes. One of these cases treated twenty-five years ago with old tuberculin recovered and is still alive.

As atypical Hodgkin's we designate cases in which the atypical myeloid cells, "Dorothy Reed" cells and eosinophiles are either few in number or absent. The focal or nodular replacement of the lymph-nodes by fibrous connective tissue, or atypical lymphoid tissue, with all of the clinical picture of Hodgkin's, constituted the basis for the diagnosis of Hodgkin's and clinical observation confirmed this in the majority of these cases. Of a few cases in which biopsies were secured months or years later, some showed typical Hodgkin's lesions, others the microscopic picture of lymphosarcoma or reticulocytosarcoma; for the greater part this group represents transition forms to the sarcomatous type of lesion, and we would today place them in this category.

By sarcomatous Hodgkin's we mean very actively growing, diffusely cellular rather than nodular lesions, with few or no eosinophiles or Dorothy Reed cells, and a greater tendency to infiltrate and to metastasize, particularly in the kidneys and lungs. The sarcomatous transformation of a Hodgkin's may proceed in one of two directions, either leading to a lymphosarcoma or to a large-celled form, with abundant reticulum and numerous giant cells, which we have styled a reticulocytoma or reticulo-endothelioblastoma. The former arises through the overproduction of maternal lymphoblasts, the resulting growths being typical lymphoblastomas (lymphosarcomas), either small celled or large celled. All lymph-node structure is lost, the germ centres and sinuses disappear, cortex and medulla become converted into a uniform mass of atypical lymphocytes with many large maternal lymphoblasts scattered throughout, and there is an infiltration of the capsule and pericapsular tissues. Ultimately, in place of the Hodgkin's lesion all of the lymphoid tissues of the body assume the character of the lymphoblastoma. In twelve of our cases repeated biopsies showed the progress of this transformation from a typical Hodgkin's to a typical lymphoblastoma, with com-

plete absence of eosinophiles, giant cells, myeloid cells, and disappearance of the reticulum. Usually the resulting lymphoblastoma is aleukæmic, but in six of our cases there gradually developed the blood picture of a lymphatic leukæmia. In the reticulo-endothelioblastoma form, the lymphoid cells become reduced in number, the eosinophiles disappear, and the majority of the cells come to be large polymorphic cells with abundant cytoplasm, and possessing many large hyperchromatic nuclei. Numerous giant cells of the myeloid type occur, and the appearances may be those of a large round-cell sarcoma of malignant type. The reticulum is usually very abundant and prominent, forming an interlacing network of coarse fibrils in the spaces of which lie the sarcoma cells. This form shows a greater degree of malignancy than either the type Hodgkin's or the lymphoblastoma. It is especially likely to develop metastases in the kidneys, and the spleen is involved earlier than in the other two forms. In some cases a rapid enlargement of the liver results

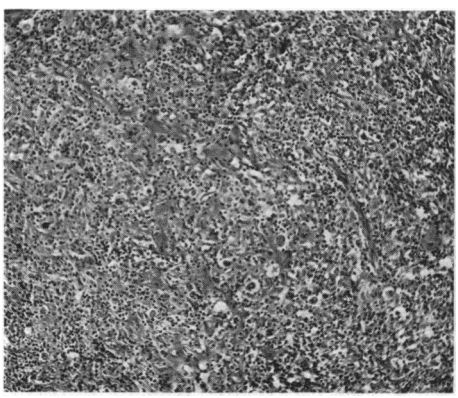


FIG. 1.—Transformation of a Hodgkin's into a reticulocyto-endothelioblastoma. Ultimately all traces of the Hodgkin's lesion disappeared.

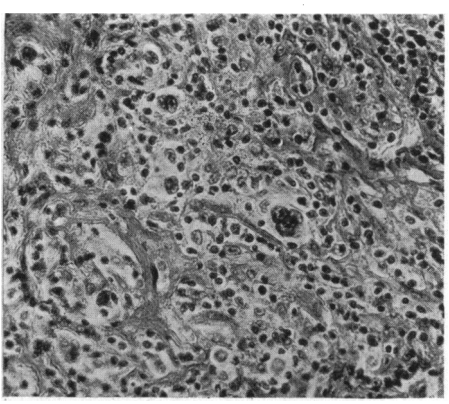


FIG. 2.—Sarcomatous Hodgkin's. Transformation into reticulocyto-endothelioblastoma.

from the marked infiltrations of the periportal tissues. In our material there were twenty-nine cases of this type of sarcomatous Hodgkin's, and in a number of these the process has been followed in successive biopsies extending over a number of years, in one case over seven years (controlled by X-ray irradiation). We have seen one case of this type proceed to a rapidly fatal termination in a child just over one year of age, the lesions presenting from the beginning the histologic picture of the reticulo-endothelioblastoma. Without irradiation the clinical course of this type is usually more malignant and shorter. Finally, in irradiated cases of Hodgkin's, after some years, the Hodgkin's lesion may be replaced by the sarcomatous, and the case be brought to a speedy termination. In the one case of Hodgkin's mycosis fungoides seen by us, typical Hodgkin's lesions were found in the cutaneous growth and in the lymph-nodes. The clinical history of this case was characteristic of mycosis fungoides, with a ten-year pre-mycotic stage of skin lesions before the development of the fungating growths.

Lymphoblastoma (Lymphosarcoma).—In one hundred and thirty-four cases of biopsies from enlarged lymph-glands microscopic examination showed

the presence of typical lymphoblastoma. In the majority of these the left cervical region was primarily involved, or showed a more advanced stage of the disease. In twenty-six cases the growths were apparently primary in the gastro-intestinal tract. Nineteen cases were diagnosed in the routine examination of tonsils, and later showed enlargement of the cervical nodes. One of these cases lived for seventeen years after the diagnosis had been made upon his enlarged tonsil, dying ultimately of generalized lymphoblastoma. Another case lived for thirteen years after the tonsil diagnosis, dying with generalized lymph-node enlargement. In both of these cases the extension of life was undoubtedly due to the systematic use of X-ray irradiation. Microscopically, all of these cases presented the same histologic picture, an atypical diffuse lymphoid hyperplasia (usually small celled) with loss of germ centres and normal architecture, and with infiltrations extending beyond the capsule of the node. The majority of these growths were medullary and

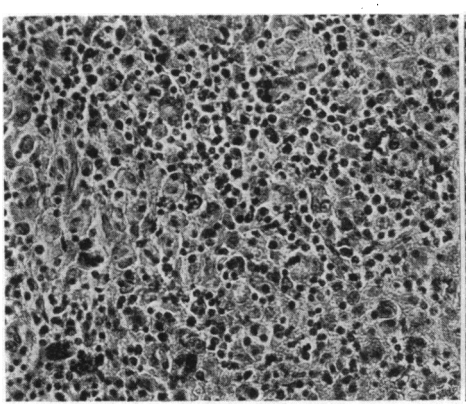


FIG. 3.—Sarcomatous Hodgkin's. Transformation into lymphoblastoma.

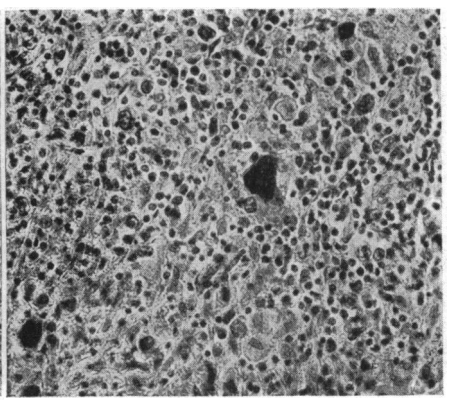


FIG. 4.—Transformation of a Hodgkin's to a lymphoblastoma. Traces of Hodgkin's foci still persistent.

showed but little stroma; in only a few was there an abundant stroma. In the latter the cells were often of the type of large lymphocytes, rather than of the small lymphocyte. The majority of these cases of lymphoblastoma showed clinically more or less febrile reaction, resembling that in the Hodgkin's cases. Similar degenerative changes (necrosis) occurred also in the enlarged nodes. Nine cases showed a transformation from the aleukæmic stage to the leukæmic. In the twenty autopsy cases of lymphatic leukæmia practically the same glandular lesions were found as in the twenty autopsy cases of aleukæmic lymphoblastoma. In both forms the kidneys usually presented large and numerous metastases, the liver showed marked lymphoblastomatous infiltrations of the periportal tissues, and the spleen showed a diffuse lymphoblastomatous metaplasia. Infiltration in the retroperitoneal adipose tissue and in the lungs also was frequent. In several cases of the large-celled form coming to autopsy emboli of large atypical cells were found in great numbers in the pulmonary, liver, splenic and renal vessels. In forty-four of the biopsy cases a diagnosis of atypical lymphoblastoma was rendered

because of combined features of Hodgkin's and lymphoblastoma, or of reticulo-endothelioblastoma and lymphoblastomatous hyperplasia. In our experience the response to X-ray irradiation of the aleukæmic form of lymphoblastoma has been on the whole much better than in the case of Hodgkin's, but even after several years of apparent disappearance of the enlarged nodes recurrence takes place with a fatal ending.

Mycosis Fungoides.—In the great majority of cases this disease is a small-celled lymphoblastoma involving the primitive lymph-nodes of the papillary layer of the dermis, but ultimately coalescing to form the fungoid tumors of the skin, becoming generalized at last in all of the lymphoid tisues of the body, lymph-nodes, spleen, bone-marrow and thymus, and presenting the same periportal infiltrations in the liver, and renal metastases that are characteristic of primary lymphoblastoma of the regional lymph-nodes. It also may become leukæmic, or may be associated with a leukæmia from the beginning

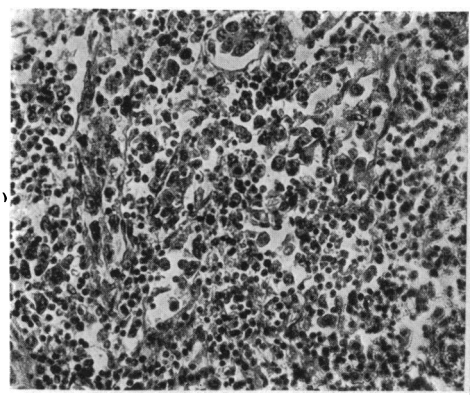


FIG. 5.—Lymphoblastomatous transformation of Hodgkin's. Biopsy two years previously showed typical Hodgkin's. Present biopsy showed complete disapearance of Hodgkin's lesion, with replacement by lymphoblastoma. Confirmed by further biopsies.

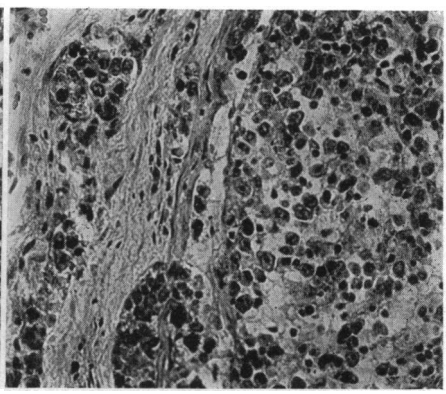


FIG. 6.—Lymphoblastomatous transformation of Hodgkin's disease. Infiltration of neoplastic process through capsular blood-vessels.

(leukæmia cutis). In one of our cases coming to autopsy the infiltrations in the skin were typically those of Hodgkin's disease; in another the cells were chiefly of the plasma-cell type; in another they were myeloid in character, while in another case the infiltrations and the skin tumors consisted chiefly of eosinophile cells, mostly mononuclears. Aside from the skin involvement, which may precede or follow that of the regional lymph-nodes, the pathologic picture is that of a generalized lymphoblastoma. When primary in the primitive lymph-nodes of the skin the development of the disease may be very slow; a "pre-mycotic stage" of several years' duration may precede the development of actual tumors in the skin. In our material there were twenty-three cases of the aleukæmic form of lymphoblastoma, and five cases showing a transformation from the aleukæmic to the leukæmic stage, while three cases were of the leukæmic cutis type from the beginning of the process. Other observers have noted the occurrence of the Hodgkin's type of lesion in the cutis, but the writer has found no reported case of the eosinophilic form. It is possible that some of the cases diagnosed clinically

as multiple hæmorrhagic sarcoma of Kaposi may be related to mycosis fungoides. In our material we have had but one biopsy from such a case, and the microscopic picture appeared indistinguishable from that of the early pre-mycotic stage of mycosis.

The above brief analysis of our material forms the foundation upon which the following conclusions are drawn:

1. Hodgkin's disease, sarcomatous Hodgkin's, aleukæmic and leukæmic lymphoblastoma, aleukæmic and leukæmic mycosis fungoides are all true neoplasms and are genetically closely related.

2. Transition forms between all of the types exist.

3. They differ chiefly in the degree of entdifferentiation shown by their cell types, and in their point of origin.

4. They all take their origin from perivascular reticulo-endothelium, or the maternal lymphoblasts of the lymphoid tissues of the body.

5. Those arising from the hæmatopoietic perivascular reticulo-endothelium take on the type of Hodgkin's, sarcomatous Hodgkin's (reticulocyto-endothelioblastoma), or even of myeloid forms of sarcoma. Those arising from the maternal lymphoblasts have the character of the lymphoblastoma, small-celled or large-celled, aleukæmic or leukæmic. The maternal lymphoblasts are derived from the same perivascular reticulo-endothelium, but represent a higher stage of differentiation than do the Hodgkin's and the reticulocyto-endothelioblastoma forms. The sarcomatous Hodgkin's of the reticulocytoblastoma type represents a greater entdifferentiation than the Hodgkin's type; while the lymphoblastoma represents a higher stage of differentiation.

6. The more undifferentiated forms, Hodgkin's, sarcomatous Hodgkin's and typical lymphoblastoma forms occur chiefly in individuals of younger ages; while the typical aleukæmic and leukæmic neoplasms are more frequent in older individuals.

7. They all run a similar clinical course, often with fever, characterized by remissions and recurrence of the tumors, with the development of a progressive tumor cachexia, anæmia, emaciation and prostration. No case has ever been cured; when removed surgically the regenerated glands become similarly involved in the process. While suggesting analogies with chronic infectious processes, they differ from these in that no mild or cured cases occur, there is no evidence of any immune reaction on the part of the organism, and the process shows a steady malignant progression to the fatal termination.

8. Pathologically, the lesions are neoplastic in type, rather than granulomatous; they show true infiltrations and metastases. In their cell types and architecture they follow definite patterns which cannot be explained on the basis of an inflammatory reaction.

9. There is but one method of treatment, which will delay, but will not halt, the inevitable malignant progress of these growths, and that is the judicious and systematic employment of X-ray irradiation.