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TUMORS AND TUMOR-LIKE CONDITIONS OF THE LYMPHOCYTE, THE MYELOCYTE, THE ERYTHROCYTE AND THE RETICULUM CELL *

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During the seven years that the Lymphatic Tumor Registry ‡ of the American Association of Pathologists and Bacteriologists has been operating 380 cases have been contributed. Fifty of these cases were not tumor or tumor-like conditions of either lymphatic, hemopoietic, or reticulo-endothelial tissues. Of the balance all are of interest and value in the study of these conditions, but only about half of the total number have sufficiently complete records and material to permit the defining of the conditions present. Therefore, too few cases have as yet been contributed to the Registry to make statistical study of the individual conditions of much value in determining the age distribution, clinical character, course and outcome of each type of lesion. The cases most valuable to the Registry are those that have been followed to their conclusion, autopsy performed, and material furnished from biopsy and autopsy.

All cases in the Registry have been reviewed each year by the Registrar preliminary to rendering the annual report. All cases offering definite difficulties in diagnosis, in which adequate data and ma-

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‡ The Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists was established in 1925. It is now the Lymphatic Tumor Division of the American Registry of Pathology maintained at the Army Medical Museum under the auspices of the National Research Council. The committee for the Association consists of Dr. F. B. Mallory and Dr. James Ewing, to whom all difficult cases are referred. The author is Registrar and here expresses his deep appreciation for the invaluable coöperation of the committee, but assumes the entire responsibility for the opinions herein expressed.

terial were available, have been referred to the consulting committee and often to other pathologists. As a result of these studies points of importance in differential diagnosis have been brought out and it is believed that their presentation at this time may stimulate thought and discussion to the end that we may arrive at a classification of the tumor and tumor-like conditions of the lymphatic, hemopoietic and reticular tissues.

The nomenclature of these conditions in the textbooks and articles in periodicals is extremely variable, and there is a like variation in the nomenclature in the diagnoses received from the committee and from others who have examined the material. As is true of tumors of any structure there are many atypical cases, but there is little agreement in terminology. The data and illustrations in the literature are rarely adequate to define the entity presented, so that published reports have been found of little value in establishing a standard nomenclature. The cases forming the basis of this report are not all complete but were selected as conforming to types of which there are a sufficient number to be of value in classification.

In this discussion it is not considered wise to enter into the controversy concerning the ultimate origin of the cells concerned, but rather to consider the adult cell and attempt to define the conditions that arise from it. For this purpose the following stem cells each form a group and each group is subdivided into the types that appear to be represented in the Registry collection. These are the stem cells giving rise to the *lymphocyte*, the *polymorphonuclear leukocyte*, the *red blood corpuscle*, and the *monocyte* or reticulo-endothelial cell. It is realized that exception will be taken to the inference that the monocyte and the reticulo-endothelial cell are one and the same or that they have a common origin, but these neoplastic conditions present certain indications that such is the case.

It is not believed that there are any concepts in this article that have not been presented or at least suggested before. To trace these for priority of publication is beyond the energy of the writer and the scope of this article.

Lymphocyte

I. Lymphocytosis: Lymphoma

Unless the term *lymphoma* is applied to inflammatory reactions there are no cases in the Registry.

TABLE I

Classification of Tumors and Tumor-like Conditions of the Lymphatic, Hemopoietic and Reticular Tissues

Adult cell type	Lymphocyte	Myelogenous		Reticulum cell	
		Granular leukocytes	Red blood corpuscles	Reticulocyte monocyte	Hodgkin's disease
I† Reactions	*"Lymphoma" Lymphocytosis	Leukocytosis	Symptomatic polycythemia	*Gaucher's disease Niemann-Pick disease	Localized (sclerosing)
II Proliferations of neoplastic type	Leukemic lymphocytoma 1. Chronic 2. Acute	Leukemic myelocytoma 1. Chronic 2. Acute	1. Polycythemia vera (Syn. Erythremia 2. Leukemic erythrocytoma	Leukemic reticulocytoma (Syn. Monocytic leukemia)	←
III	Aleukemic lymphocytoma 1. Diffuse 2. Nodular	Aleukemic myelocytoma 1. Single 2. Multiple (Syn. Multiple myeloma)	*Aleukemic erythrocytoma	Aleukemic reticulocytoma	Generalized (cellular)
IV Malignant tumors	Lymphosarcoma 1. Aleukemic 2. Leukemic (Syn. Lymphatic leukosarcoma)	Myelosarcoma *1. Aleukemic 2. Leukemic (Syn. Myelocytic leukosarcoma) Chloroma	Erythrosarcoma *1. Aleukemic 2. Leukemic	Reticulum cell sarcoma	Sarcomatous

* Type not observed in Registry.

† Roman numerals refer to text heading.

II. Lymphocytoma, Leukemic — Syn. Lymphatic Leukemia

1. Definite leukemia, 25,000 or more white blood cells with a preponderance of lymphocytes. The number of cells varies in the individual case and from time to time in the same case. Also, cases that primarily are classified in the aleukemic group (below) may become leukemic and remain so, either after irradiation or spontaneously. The type of cells may be uniform or considerable variation may occur. The more numerous the younger forms, the more rapid the course of the disease and usually the younger the patient.

2. The enlargement of lymph nodes is usually generalized and the spleen, or liver, or both, usually are more or less increased in size. There may be an area of greater enlargement, especially in those cases in which the enlargement is the first symptom noted. This is true of those cases of aleukemic lymphocytoma that later become frankly leukemic. In general, the greater the number of lymphocytes in the blood the less the swelling of lymph nodes, and *vice versa*.

3. Microscopically there is an increase in the size of the primary nodules, due to proliferation of the lymphocytes. This proliferation finally obliterates the node structure so that it becomes a uniform mass of lymphocytes. In the liver the portal spaces are distended or enlarged by lymphocytes which also infiltrate between the liver cords. In the spleen the malpighian nodules are enlarged and encroach on the red pulp, often apparently obliterating it. In other organs diffuse infiltrations occur but these, even when grossly visible as pale areas, appear to be proliferations starting in preëxisting collections of lymphocytes. In this condition there are no true metastases. These infiltrations are more frequent and larger in the acute forms of leukemia. Some cases show many atypical cells and then approach the sarcoma type. Occasionally, cases primarily leukemic terminate in typical metastatic lymphosarcoma.

4. The reticulum of the nodes is not increased but is distended or separated by the lymphocytic increase.

5. Irradiation is effective in reducing the size of the tumors and the number of cells in the circulating blood. In many cases it appears to have increased the duration of life but it is only a palliative treatment and not curative.

III. Lymphocytoma, Aleukemic — Syn. Lymphatic Pseudoleukemia

(*a*) *Diffuse Type:*

1. Leukemia is absent but there are always abnormal lymphocytes in the blood if proper search is made for them. At times, and often throughout the course of the disease, there is an actual increase in lymphocytes. It is difficult to make a dividing line between the aleukemic and leukemic forms, as these merge into one another and the aleukemic form may become leukemic and, rarely, cases which when first observed have a leukemia of 25,000 or more may become aleukemic. For the purpose of this classification 25,000 or more white blood cells, with a preponderance of lymphocytes, have been considered necessary for the diagnosis of leukemia.

2. The swelling of the lymph nodes is less generalized than in the leukemic form and there is usually a region of greatest intensity. The spleen, or liver, or both may participate in the process.

3. Histologically the picture in the nodes may be the same as in the leukemic form, or a group of nodules may coalesce and leave some relatively unchanged node structure. This is especially true of the more rapid, fatal processes at the younger ages in which the cells often appear to be of unusually large size and show relatively frequent mitoses. Infiltrations are unusual and when present indicate an approach to leukemia or the presence of a leukemic change unrecognized before. It is not unusual to find evidence of a definite leukemia at autopsy, which had not been discovered in blood examinations. It represents a change subsequent to the blood examination last recorded and may have taken place within a few days of death. When atypical cells or many mitoses are found the condition approaches that of a lymphosarcoma which is sometimes the terminal picture in this group.

4. Reticulum the same as in the leukemic form.

5. Irradiation is effective in reducing the size of the nodes as a palliative measure. Following X-ray these cases may become leukemic.

(*b*) *Nodular Type — Syn. Giant Follicular Hyperplasia with Splenomegaly:*

1. The blood changes are similar to those in the diffuse form (above) but apparently leukemia develops less frequently.

2. The swelling of the lymph nodes is the same as in the diffuse form and is sometimes quite generalized. The spleen has always been involved, and in two observed cases was apparently the only focus of the disease.

3. Histologically the condition is characterized by large nodules, which appear to be of a secondary type, and an apparent increase in their number. The nodules are composed of the large type of lymphocytes, among which are rather numerous mitotic figures. The nodules may be contiguous and rarely appear to have coalesced, though there is often marked variation in size in the same section. These nodules are surrounded by relatively normal lymphocytes of the smaller size.

These individuals either die rather quickly or, if life is prolonged, the process terminates in a definite sarcomatous change in which there are metastases. In this type the cells show more pleomorphism than in any other lymphocytic tumor, resembling to some degree the cell picture of sarcomatous Hodgkin's disease, with which the condition occasionally has been confused.

4. Reticulum is loose meshed as in the diffuse form, thus differing from Hodgkin's disease or Hodgkin's sarcoma (see below).

5. This condition is very sensitive to irradiation which, properly used, will prolong life for many years. Superficial nodes well radiated may never swell again. It is quite possible that this condition may be curable when localized and treated early by adequate irradiation.

IV. Lymphosarcoma

(*a*) *Aleukemic:*

1. Typically, there are no abnormal findings in the blood, but following irradiation this form may become leukemic (see (*b*) below).

2. Tumors are localized and infiltrate, metastasize, or both. Metastatic nodules are found in situations where usually lymphocytic groups do not occur, as in the intermediate zone of the liver, the lower cortex of the kidney and the heart muscle.

3. Histologically the tumor itself is made up of atypical lymphocytic types with irregular nuclei and scanty cytoplasm. Mitoses are usually abundant. The more atypical the cells, the more malignant the tumor. Following irradiation the cells may become more typical.

4. Reticulum is loose meshed, as in the preceding types.

5. Very sensitive to irradiation, so much so that it is possible that taken early and adequately treated the tumor may be cured.

(*b*) *Leukemic — Syn. Lymphatic Leukosarcoma:*

1. Leukemic blood with a considerable proportion of abnormal young or embryonal types of lymphocytes. The leukemic condition in lymphosarcoma may be spontaneous, may follow irradiation, or a leukemia may terminate in a sarcomatous spread.

2. Local tumor mass invading, metastasizing, or both, with metastatic nodules as in the aleukemic form. In addition gross infiltrative types of spread may be found, as in ordinary leukemia.

3. Histologically the cells are atypical, as in the aleukemic form. In those cases that are primarily aleukemic but become leukemic after irradiation the cells become more typical.

4. Reticulum as in the other lymphocytic groups above.

5. Sensitive to irradiation to some degree but many cases terminate so quickly that no adequate data have been accumulated. The cases that have become leukemic after irradiation appear to be less sensitive than the aleukemic form and it is possible that the leukemic change in these is the result of inadequate or improper irradiation dosage.

The group of conditions arising from the lymphocyte or its stem cell is the best defined and best understood of all the groups here considered. The term lymphoblastoma may be applied to the entire group, but the different members must be otherwise designated as the term does not sufficiently define the entities. As there are no benign, non-inflammatory lymphomas in the Registry the criteria have been omitted but the condition has been placed, together with lymphocytosis, in the reactive group. Lymphocytosis is represented by several cases of glandular fever, the cell picture of which is that of a lymphocytic proliferation with active hyperplasia of the secondary nodules.

The rest of the group is familiar to most, under a variety of names which sometimes vary because of minor cytological or clinical differences, though more often nomenclature depends on previous instruction, either undergraduate or postgraduate. The simplest and shortest terms have been preferred in this work and the prefix "a" is sufficient to differentiate the leukemias from those conditions that are quite similar except for the absence of an appreciable increase of

cells in the peripheral blood. The term pseudoleukemia, also, is quite acceptable as accurately descriptive. The term "aleukemic leukemia" certainly has nothing to recommend it, even though there are phases in leukemias during which the leukemia is diminished or absent. Such phases, whether the result of treatment or not, can be designated as such without the use of a name suggesting a change to a different disease.

In this group arising from the lymphocyte there is considerable shifting from one subdivision to another, both spontaneously and as a result of irradiation. For instance a leukemia may terminate in a lymphosarcoma, or may become aleukemic. Leukemic or aleukemic lymphocytoma may become sarcomatous. In all aleukemic cases in the Registry from which blood films have been furnished abnormal lymphocyte types have been found, while frequently during the course of the disease a definite lymphocytosis is present even though a frank leukemia never appears.

Lymphosarcoma usually appears and continues as such. Occasionally, as indicated by the literature, a combination of a metastasizing tumor and a leukemia occurs (leukosarcoma) and may be the condition discovered at primary examination. In the Registry material a condition of leukemia has followed irradiation of lymphosarcoma in six instances and in these the progress of the disease has appeared to have been retarded as a result of the change.

The liver is an important organ to study in the differentiation of types. In the lymphocyte group there is a general proliferation of the lymphocytes in the portal areas, increasing the size of these areas either with or without infiltration between the liver cords. The infiltration is present in leukemia and this finding at autopsy always suggests that whatever may have been the findings in the blood a leukemic condition had existed perhaps only near the termination of the illness.

In this classification the extension of the process to other nodes or lymphocytic tissues is not considered a metastasis. Whether this spread is the result of a stimulus in the circulating blood or whether it is due to cells from the original process reaching the new areas by blood and lymph, and there only finding satisfactory conditions for growth, is not known. The latter alternative seems the more probable method.

Granular Leukocyte

I. Leukocytosis of the Granular Leukocytes

II. Myelocytoma, Leukemic — Syn. Myelogenous Leukemia

1. Definite leukemia, 25,000 or more white blood cells with a large proportion of myelocytes. The number of cells in the blood varies over a rather wide range even in a single case, and there is also a variation in the relative proportions of the different myelocyte types. In some cases, with or without treatment, the number of cells may decrease to a very low total, though more often the reverse is true. The greater the variation in cell type, usually, the more rapid the course of the disease.

2. The bone marrow shows marked myelogenetic activity and, therefore, there is a decrease in the red marrow. The spleen is markedly enlarged in most cases and the nodular markings are obscured. The liver is also enlarged to varying degrees. Lymph nodes usually do not participate in the swelling. Sometimes infiltration deposits are visible grossly in the tissues.

3. Microscopically there is marked myelogenetic activity in the bone marrow. The proliferating cells replace the marrow fat and crowd the erythrogenetic tissue. There is no bone destruction. In the spleen myelogenesis is usually active and takes place in the red pulp. It crowds and compresses the malpighian nodules and practically obliterates some of them. In the liver there is a diffuse infiltration, usually somewhat more marked in and near the portal connective tissue, but there is no great enlargement of these areas. Infiltration is more or less generalized and often relatively large masses are formed which suggest metastatic tumor. Where lymph nodes appear enlarged the histological picture is that of an infiltration, as in other organs. Occasionally leukemias become definitely sarcomatous and thus would be finally classified in Group IV, below.

4. There is no increase in reticulum in the marrow, though the spleen, especially after irradiation, shows some increase in fibrous tissue.

5. Irradiation is effective as a palliative measure in many cases. In the more acute forms it often appears materially to retard the process.

III. Myelocytoma, Aleukemic ((a) Single, (b) Multiple) — Syn. Single and Multiple Myeloma

1. Aleukemic but young cells are usually present in the blood and leukemia may occur during the course of the disease.

2. (*a*) Single myeloma occurs in long and flat bones where it produces definite tumors of osteolytic type without much tendency to spontaneous fracture.

(*b*) Multiple osteolytic tumors of the marrow, destroying the bone from within and leading to spontaneous fracture which is often the first definite symptom.

In both single and multiple myeloma there are no true metastases, though the invasiveness of some of them approaches the sarcoma type and sarcomatous changes may occur and metastases take place.

3. Microscopically the cells composing these tumors show considerable variation between different cases but tend to be rather uniform in the individual case. The most uniform picture is that of the so-called plasma cell type which is found in both the single and multiple form. Others show some variation in cell size and staining characteristics. Variation in size is an indication of greater malignancy, an approach to the true sarcoma in which there may be extreme variation in size and form.

4. No reticulum is produced by the tumor cells, though there is some supporting reticular tissue accompanying blood vessels.

5. These tumors are sensitive to irradiation but to what degree cannot be decided by the few cases in the Registry.

IV. Myelosarcoma

(*a*) *Aleukemic:*

This has not been observed in the Registry material. It is possible that this form is represented by those cases of single and multiple myeloma that invade other tissues without metastasis. The metastatic myelogenous neoplasms in the Registry have all been leukemic.

(*b*) *Leukemic — Syn. Myelocytic Leukosarcoma:*

This group includes the "green" tumor, chloroma.

1. The blood shows a definite leukemia in which there are many embryonal types of cell. The total count varies but is not often as high as in the chronic leukemias.

2. Aside from the bone marrow changes, which may be evenly generalized or have a focus of greater intensity, there are growths from the bones into adjacent tissues and metastatic deposits in parenchymatous organs. The primary spread from the bone, the metastases, or both, may show the green color characteristic of chloroma.

3. The cells are always more varied in form and staining than in the non-sarcomatous type and if a sarcomatous change occurs in a case of simple leukemia there may be found a definite focus of sarcoma type in the bone, surrounded by the usual picture found in simple leukemia.

4. Reticulum is not formed by the tumor cells.

5. Radiation sensitivity not determined by Registry material or literature. Theoretically this group should be sensitive to irradiation, but the course is usually so brief that no adequate data are available.

The stem cell for the granular leukocyte gives rise to the myelogenous, myelocytic leukemias, the aleukemic myelomas and the myelosarcomas or metastasizing myelocytic tumors. This group shows less shifting from one group to another but occasionally a sarcomatous change occurs in a myelogenous leukemia and likewise a leukemia may develop in an aleukemic myeloma. The principal difficulty in this group is the question as to which types are sarcoma. Both single and multiple myelomas destroy bone and by this invasiveness to some degree merit the term of sarcoma; but, the lymphocytomas by pressure may destroy neighboring tissues and the cells invade the repair-like process at the periphery of the growth. When single or multiple myelomas break through the bone and invade surrounding tissues they may be considered as truly malignant and therefore could be considered as belonging to the group of aleukemic myelosarcomas.

Aside from the multiple myelomas the sarcomatous myelocytomas in the Registry have all been leukemic. Chloroma is represented. The green pigmentation is occasionally present in the more malignant myelomas without leukemia.

In the leukemias the infiltrations are difficult to differentiate from true metastases. It is of little practical importance to make this differentiation. Infiltrations are usually more frequent and extensive in the cases clinically more malignant.

In the liver infiltrations are more prominent in and near the portal areas, but masses of considerable size are not found, as in the lymphocytic type. Sometimes lymph nodes show considerable enlargement as a result of infiltrations. Such infiltration is diffuse and the architecture of the node is preserved.

In myelocytic leukemia the blood film often shows considerable numbers of immature red corpuscles and nucleated cells of the "blast" type. This appeared to be compensatory, or at least consistent with the idea that parts of the marrow are forced to overwork and throw out immature forms in the effort to compensate for marrow destruction or replacement by the granular myelocytic proliferation.

Red Blood Corpuscle

I. Polycythemia, Symptomatic

An increase in the red corpuscles of reaction origin due to some definite and readily determined cause, such as being in high altitudes.

II. (a) Polycythemia Vera — Syn. Erythremia

This condition is suggested for this position as the analogue of chronic types of leukemia.

1. Increase of red corpuscles in the blood. Platelets are increased and, especially in the later stages, there is an increase in granular leukocytes which might be considered as analogous to the appearance of considerable numbers of "blasts" in myelocytic leukemia.
2. The bone marrow shows erythropoietic hyperplasia. The spleen is enlarged, usually with relatively little evidence of erythrogenesis. The enlargement appears to be due to the increase in blood corpuscles in the red pulp.
3. Reticulum of the organs concerned shows no change.
4. Irradiation is apparently of little benefit.

(b) Erythrocytoma, Leukemic — Syn. Erythrocytic Leukemia

This condition, a leukemia of the precursors of the red blood corpuscles, the erythrocytes, is the analogue of the acute leukemias; that is, those in which a large proportion of the cells are of more embryonal type than those normally found in the circulating blood.

1. Definite leukemia, the cells of which resemble lymphocytes, have little cytoplasm, often appearing as naked nuclei. Many "blasts" are present, the larger types predominating. Many abnormal red corpuscles.

2. Bone marrow shows marked erythropoiesis, the yellow marrow being replaced. The spleen is enlarged sometimes to a considerable degree. Lymph nodes are sometimes slightly enlarged, particularly those of the abdomen.

3. Microscopically in the marrow there is a replacement of the fat by embryonal cells of the erythrogenetic group, with an apparent crowding of all normal marrow cells. Even the strands of erythrogenetic tissue seem less numerous than normal. The predominating cell is polygonal with a vesicular nucleus and considerable cytoplasm which is non-granular. The spleen shows a productive type of process in the red pulp, in which erythrogenesis appears to be active. Lymph nodules are crowded by the infiltration or proliferation and some appear to be obliterated. In the lymph nodes there is an infiltration between the lymph nodules and, in this infiltration and in the spleen, megakaryocytes in all stages of development are usually found. These cells in certain stages of development may be confused with the Dorothy Reed cells and a diagnosis of cellular Hodgkin's disease made.

4. No new reticulum is formed.

5. Irradiation sensitivity — no data.

III. Erythrocytoma, Aleukemic

There are no cases of this type in the Registry. The condition of erythroblastic anemia seen in the earlier age groups appears to satisfy the requirements of this position.[2]

IV. Erythrocytic Sarcoma

(*a*) *Aleukemic:*

Not observed in the Registry material. (See note above.)

(*b*) *Leukemic:*

This condition was distinguished from the leukemic erythrocytoma by the presence of metastases in the one case that has been observed. These metastases were small hemorrhagic nodules of erythrogenetic tissue.

The group of conditions arising from the stem cell of the red corpuscles is of particular interest because so few cases have been recognized. In this study the writer has used the term erythrocyte to indicate the nucleated form preceding the cell which after loss of its nucleus becomes the corpuscle. Other terms are difficult to adapt, but it is realized that erythrocyte is used as a synonym for red blood corpuscle.

In this group few will disagree with the placing of symptomatic polycythemia in the reactive position. It is also possible that eventually all cases of polycythemia vera, erythremia, can be so placed, but the blood, marrow and spleen in cases of erythremia are analogous in their enlargement and activity to the picture seen in chronic myelocytic leukemia. Careful study of the blood in erythremia occasionally shows blasts, while among the leukocytes are usually found atypical mononuclear cells which cannot be definitely placed in the myelocyte group.

The analogue of acute leukemia in this group is characterized by a leukemia of non-granular cells having little cytoplasm and which cannot readily be differentiated from embryonal lymphocytes. In addition, however, there are numerous "blast" types and many abnormal corpuscles. The bone marrow in general is red, but with pale areas or large involvements of solid tumor-like tissue replacing the normal marrow. In the spleen the change or proliferation is in the red pulp, there being no proliferation of the malpighian nodules.

In the spleen and to some extent in the lymph nodes there is active erythropoiesis, which in the nodes appears as a part of an infiltrative process composed of undifferentiated cells, erythroblasts and a diffuse infiltration of the mature forms, the red corpuscles. Except for the type of cell the picture is that of a myelocytic condition. Hasty examination of the blood film usually leads to a diagnosis of acute lymphatic leukemia. The marked tendency to hemorrhage and the large number of "blasts" in the film are the clues that suggest the correct diagnosis. The formation of typical adult megakaryocytes in the affected tissues is of value but also seems to confuse the condition with Hodgkin's disease. The lack of sclerosis and the infrequency of typical Dorothy Reed types is of assistance in differentiation. In the nodes the fact that the process is infiltrative and does not show proliferation of the lymphocytes of the nodules or the internodular stroma is an important differential point.

The Reticulocyte (Monocyte)

Certain reactive conditions show such a preponderance of reticular hyperplasia that they are placed in this group rather than in that of the lymphocyte. These include tuberculosis, leprosy, tularemia and some others. Hodgkin's disease is characterized by a reticular hyperplasia and the so-called Hodgkin's sarcoma is a reticulum cell sarcoma which shows more cellular pleomorphism than the typical reticulum cell sarcoma. However, as there is so much controversy as to whether the conditions generally diagnosed Hodgkin's disease are reactions to infection or are neoplasms, they are placed in a separate column but under the heading designating conditions of reticulum cell hyperplasia.

I. Reactive Reticulocyte Hyperplasias

Examples are tuberculosis, leprosy, tularemia, and possibly the conditions of unknown etiology — Gaucher's and Niemann-Pick disease, which appear to be hyperplasias of reticulum cells.

II. Reticulocytoma, Leukemic — Syn. Monocytic Leukemia

The existence of this condition is now well established. Only one case is included in the Registry.

1. Leukemia of large cells of monocyte type having oval, bean-shaped or irregularly lobed nuclei and considerable basophilic pale cytoplasm. These cells are most difficult to separate from myelocytes, and differentiation by the blood film depends on precise staining. The cytoplasm is more abundant than in myelocytes, the size is more uniform and good staining brings out their essentially non-granular character. Accentuation of the acidophilic dye may show fine granules close to the nucleus. Too few cases have been observed to make further suggestions as to their differentiation, but the vital stains should be of value.

2. The spleen, lymph nodes and lymphatic structures are enlarged to varying degrees.

3. Microscopically there is a proliferation of rather typical reticulum cells between the nodules of lymph nodes and at the periphery of malpighian nodules in the spleen. The lymphatic nodules are not increased in size. Mitoses in the case observed were rare.

4. The proliferation is characterized by a delicate meshwork of reticulum closely surrounding the individual cells.

5. Irradiation — no available data.

III. Reticulocytoma, Aleukemic — (Usually Termed Reticulum Cell Sarcoma)

1. The blood is aleukemic, though there may be an increase in monocytes, particularly after irradiation.

2. Enlarged lymph nodes without true metastasis.

3. Microscopically there is a diffuse hyperplasia of reticulum cells obliterating the node structure, with some areas and nodules of small lymphocytes remaining in the smaller and presumably more recently involved nodes.

4. Reticulum surrounds each cell, forming a delicate meshwork.

5. Sensitivity to irradiation not determined by Registry material.

IV. Reticulocytic (Reticulum Cell) Sarcoma

1. Aleukemic: Monocytes may increase in the blood following irradiation.

2. Enlarged lymph nodes, spleen, or both, with metastatic deposits, invasion of adjacent tissues, or both.

3. Microscopically the cells are atypical reticulum cells surrounded by a delicate meshwork of reticulum. The cells show varying degrees of abnormality up to extremely bizarre forms in the most malignant types. Invasiveness may be slight, but infiltrative metastases involving parenchymatous organs, and especially skin, are frequent.

4. The intimate delicate reticulum constitutes a most important differential point for the diagnosis of this condition and its separation from large-celled lymphocytomas and small-celled carcinomas.

5. Sensitivity to irradiation not determined in Registry material.

Hodgkin's Disease

There are two distinct clinical forms of this condition, which to a large extent is localized, spreads by continuity and to local lymphatic structures, and sometimes terminates in sarcoma. The other is the

generalized form which spreads to nearly all lymph node groups, to liver, spleen or both, though there is usually a focus of greater intensity or degree of swelling.

I. Localized Form

1. Blood changes not diagnostic. In febrile phases there is a polymorphonuclear leukocytosis, and particularly in the later stages or after irradiation there may be an increase in monocytes. Eosinophiles are often moderately increased.

2. Local swelling of lymph node groups with more or less fusion of the nodes. Frequent sites are neck, mediastinum and abdomen. In the thorax the process may invade the lung by continuity or extend along bronchial lymphatics. In the abdomen the liver may contain nodules here and there without generalized involvement. The spleen may contain irregular masses. Small nodes are pale pink and translucent, but soon show areas of yellowish opacity and softening. Spontaneously, and especially after irradiation, there is much fibrosis which in large amounts is almost cartilaginous in consistence.

3. The earliest changes are seen in small nodes, that is, ones recently involved by the process, as the larger nodes show such complete obliteration of their structure that the sequence of events cannot be followed. In these small nodes there is a proliferation of the reticulum of the internodular stroma and more or less proliferation of the lymphocytes of the primary nodules. Large cells are formed and later the typical multinucleated Sternberg cells. The process is usually quite definite in the internodular stroma before the proliferating reticulum cells appear in numbers in the lymph nodules, also the new reticulum is quite dense between the nodules before it invades these structures. The reticulum is gradually replaced by collagen though the remnants of the lymph nodules can usually be made out. The lymphocytes gradually decrease during this sclerosing process, which goes on more rapidly if irradiation is used. Necrosis varies in different cases and appears to start at the node periphery in the early phases. No node of small size which could be considered the starting point of a Hodgkin's process has been described. It is possible that the primary lesion is characterized by early necrosis and that the proliferative changes are secondary. These localized processes in the gross cannot be distinguished readily from tuber-

culosis, especially the extrapulmonary lymph node involvements which are not rare in the negro race. Microscopically the absence of tubercle formation and the cell picture serve to differentiate. A considerable number of eosinophiles is usually seen in the tissue, especially in the early cellular phase.

4. The proliferating cells form reticulum, which is gradually replaced by collagen in the sclerotic process. In nodes almost wholly sclerotic small areas of reticulum representing former lymph nodules are surrounded by dense, relatively acellular collagenous rings representing the internodular stroma.

5. Irradiation increases the rapidity of the sclerosis and reduces the size of the swelling, and at the same time reduces the hyperplasia, especially that of the lymphocytes.

II. (*See Reticulocytoma, Leukemic*)

III. The Generalized Form

1. Blood changes not diagnostic. Febrile attacks, as in the localized form, may be accompanied by leukocytosis of the polymorphonuclear variety, while irradiation may lead to considerable increase in the monocytes, or these cells may increase spontaneously.

2. Starting usually from some one area of enlargement of lymph nodes or spleen the process causes in a relatively short time a generalized enlargement of lymph nodes and lymphatic structures. The generalized enlargement of the liver is especially noteworthy, though not always present to a marked degree. Grossly the organ is not characteristic but often the enlarged portal areas are visible. This type remains confined to the lymphatic structures, does not invade and clinically resembles the aleukemic lymphocytoma (pseudoleukemia).

3. Histological examination shows a cellular picture with less sclerosis, especially in the form that involves the lymphatic structures of the intestine. In the liver practically every portal space shows reticulum cell proliferation with enlargement while the Kupffer cells appear to be more abundant. In the spleen the proliferation is around the malpighian nodules and sometimes extends into them and obliterates the structure. The red pulp is not affected, except by enlargement of the nodules. In the nodes the process appears to start in the internodular stroma where there is proliferation of reticulum cells, which produce abundant reticulum of looser mesh than in the

localized type. There are fewer typical Sternberg cells but the large uninucleated reticulum cells are abundant, quickly invade the lymph nodules and increase the amount of reticulum. Sclerosis is slow and in the intestinal involvements little if any collagen is laid down. Necrosis is slight or absent. Eosinophiles are rare or absent.

4. This condition is characterized by the formation of abundant reticulum. Under irradiation there is sclerosis and collagen formation, but otherwise there is less sclerosis than in the localized form.

5. Sensitive to irradiation to some degree, but the generalization of the process renders adequate irradiation impossible.

IV. Hodgkin's Sarcoma

1. No cases with leukemia have been observed.

2. Occasionally during the course of a focal or generalized Hodgkin's disease there may occur a metastasizing neoplastic process, a true sarcoma. This sarcomatous change may come early or late in the course of the disease. It is prone to occur earlier in the more cellular types of lesion and at the younger ages. It may be the termination of slow processes, particularly those of a focal or localized nature which have been kept, sometimes years, under a certain degree of control by irradiation.

3. The cell of this tumor is the reticulum cell. The microscopic picture is that of reticulum cell sarcoma, sometimes with little pleomorphism, though usually there is much more than in the typical reticulum cell sarcoma. Metastases in other than lymphatic organs show less pleomorphism and fewer infiltrating lymphocytes, though, like true lympho-epithelioma, Hodgkin's sarcoma and reticulum cell sarcoma, they usually show considerable lymphocytic infiltration.

4. The reticulum is the same as is found in reticulum cell sarcoma.

5. There are no data available on the sensitivity of this condition to irradiation.

In the monocyte or reticulum cell group the characteristic differential criterion is the production of argentophile reticulum by the proliferating cells wherever these produce tissue or, in other words, are not purely infiltrative. In lymph nodes this is best seen in the internodular stroma; in the spleen in the peripheries of the malpighian nodules. In the sarcoma types the entire node may be involved, or only a part, as in a metastasis. Most of the reticulum cell

tumors composed of uniform, atypical cells are sarcomatous in that definite metastases occur.

Group III, the aleukemic reticulocytoma, is usually considered to be sarcoma, but there are a few cases in which the lesions were confined to lymph nodes and the changes were very like those of monocytic leukemia.

Reticulum cell sarcoma really includes Hodgkin's sarcoma and it is a better term for the condition.

The two types of Hodgkin's disease described appear to the writer as quite different conditions. The localized type has all the characteristics of an infectious granuloma, more like tuberculosis than any other known disease. The generalized type is more a hyperplasia with lesions closely resembling the cellular phases of the localized form, but without the tendency to necrosis and sclerosis.

The localized form frequently shows hepatic involvement in scattered nodules or massive infiltrations, just as is sometimes seen in tuberculosis. The generalized form, however, when it involves the liver affects *all* the portal areas, the lymphatic structures of the liver, in a manner similar to the lymphocytic involvement of these areas in lymphatic pseudoleukemia.

The material reviewed is still too scanty to justify the placing of this generalized form definitely as an aleukemic reticulocytoma, but it appears quite possible that such is the case and that it is not a reactive hyperplasia. Likewise many more completed cases must be accumulated to establish definitely that Hodgkin's disease in any form is an infectious granuloma. Termination in a definite sarcomatous condition is certainly unusual for granuloma but quite frequent in hyperplasias of lymphocytic and myelocytic tissue. The search for an etiological agent is definitely outside the scope of this Registry.

Discussion

The foregoing statements are based on Registry cases in which adequate material and clinical data have been supplied. This classification is offered for criticism and to stimulate discussion and the contribution of cases which will either support, refute, or modify the opinions herein expressed.

Considerable evidence has been presented heretofore that these conditions are closely related and that there have been cases showing

transitions between the groups arising from the different cells. This is especially true of the condition termed Hodgkin's disease. There is no evidence in the Registry material that this occurs. The term Hodgkin's disease, in recent years, has been applied to conditions of various types because of the presence of large multinucleated cells, or because of the clinical similarity between the cases, just as Thomas Hodgkin confused several of the groups over 100 years ago. We have ignored the facts that practically any malignant cell in some phase of its malignancy may produce multinucleated forms and that the clinical symptoms of a neoplastic condition are dependent on the location of the involvement, rather than on the type cell of the growth. In the Registry material myelocytomas, both granulocytic and erythrocytic, reticulum cell tumors, sarcomatous and not sarcomatous, and aleukemic lymphocytomas, especially the nodular type, have been diagnosed Hodgkin's disease. It is believed that error in the original diagnosis is thus responsible for the confusion that has led to the conception that Hodgkin's disease may terminate in either the lymphocytic or myelogenous group.

As Hodgkin's disease in its malignant phase is a true metastatic tumor, or as a true metastatic tumor may develop during the course of typical Hodgkin's disease, we must determine what the cell is that forms this malignant condition. In the Registry group the cells of the metastases in the sarcomatous phase of Hodgkin's disease have produced abundant reticulum and have not conformed to the morphology of either lymphocytes, large or small, or any cell of the myelogenous group. None of the other groups, lymphocytomas or myelocytomas, both of the granulocyte and erythrocyte types, produces reticulum. Monocytic leukemias and the reticulum cell tumors produce it in abundance. In fact, many of the so-called Hodgkin's sarcomas cannot be differentiated from reticulum cell sarcoma. Hodgkin's sarcoma is often, but not always, more pleomorphic, while reticulum cell sarcoma sometimes shows considerable variation in the size and shape of the cells.

Skin lesions are occasionally found in all groups. Hemorrhagic types of lesion were present in all three cases of the erythrocyte group and are more frequent in the myelogenous than in the lymphogenous conditions.

The first phenomenon noted in reticulum cell involvements may be a skin manifestation, or the hyperplasia may appear to follow or

terminate a condition characterized by diffuse skin eruptions. Mycosis fungoides is allied to or is a type of the reactive Hodgkin's granuloma.

In general it has been found much more satisfactory to depend on the characteristics of the cell growth, its location and extension, than on the type of cell. Many of these cells cannot be distinguished from one another in the tissues, especially in the more or less atypical forms in which they occur in these tumor and tumor-like conditions.

It is fully realized that there are bizarre conditions arising from some of these cells that do now and will in the future defy classification. These often are seen in very early life and are rapidly fatal. Some may be embryonal tumors of a cell preceding any differentiation. Most of them are so malignant that death ensues before diagnosis or adequate study is made; however, most of this group of tumors and tumor-like conditions are proliferations of cells so far differentiated as to maintain certain diagnostic characteristics. Transformation of a cell that looks like a lymphocyte into a myelocyte, monocyte, and so on, may and probably does occur, but there is some doubt in such cases whether the cell was, in fact, a lymphocyte. Is it not more probable that it was a cell that could not be differentiated by the methods used?

It is of the utmost importance that adequate material, well prepared, be available for study, especially when one desires to classify the condition. A "chewed out" piece of lymph node or a poor section offers little possibility for diagnosis, except in the simplest cases. When lymph nodes are removed a large and small one both should be included. A well stained blood film is necessary.

Summary

1. A discussion of the tumors and tumor-like conditions arising from the stem cells of the lymphocytes, the granular leukocyte, the red blood corpuscle, and the reticulum cell or monocyte is presented.

2. A classification of these conditions is presented, based on a study of the cases of the Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists.

3. Certain criteria for the differentiation of the conditions are given in explanation or elaboration of the tabular presentation of the classification.

4. Certain evidence is presented that some conditions ordinarily classified as Hodgkin's disease belong to the reticulum cell group, either as reactive hyperplasias, aleukemic reticulocytomas, or reticulum cell sarcomas.

REFERENCES

1. Ewing, James. Neoplastic Diseases. W. B. Saunders Company, Philadelphia, 1931, Ed. 3, 382, *et seq.*

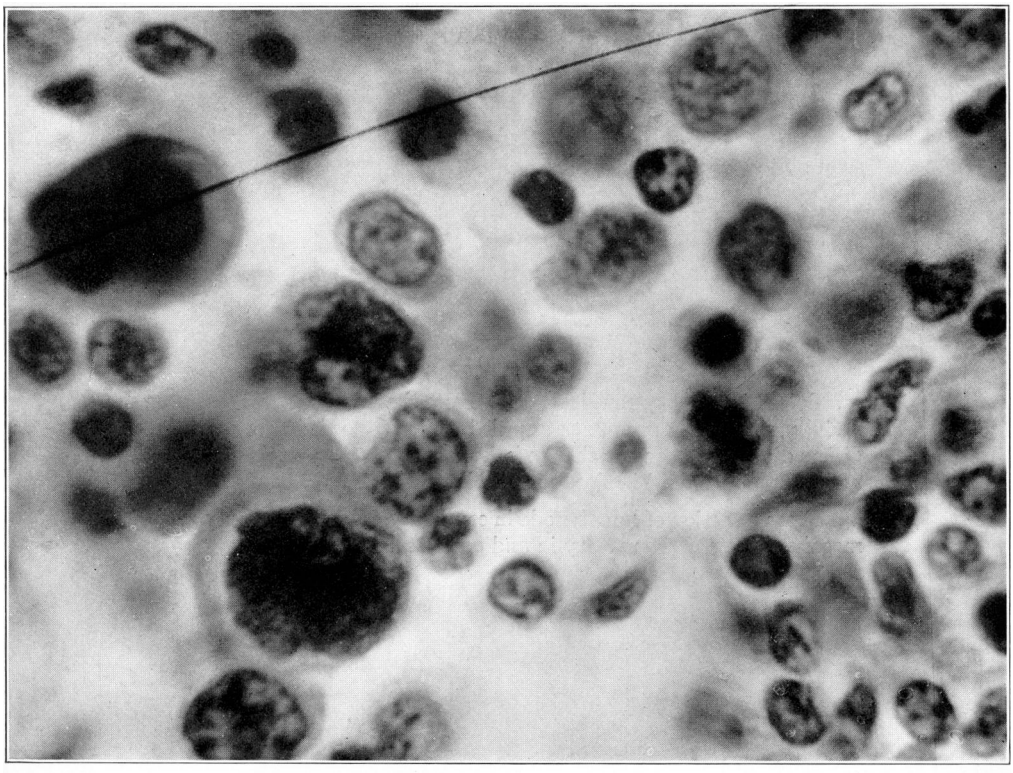
2. Ewing, James. Neoplastic Diseases. W. B. Saunders Company, Philadelphia, 1931, Ed. 3, 326.

DESCRIPTION OF PLATES

PLATE III

FIG. 1. Photograph of a section of lymph node from a case of lymphatic leukemia showing variations in cell size and giant cells. Hematoxylin and eosin stain.

FIG. 2. Reticulum stain from a section of the same node shown in Fig. 1. This is the characteristic reticulum of lymphocytic tissues. The lymphocytes do not form this reticulum. Similar reticulum is also seen in myelocytic hyperplasia. It is the normal reticulum of the node, produced by the reticulum cells. Compare with Figs. 6, 8, 10 and 12.



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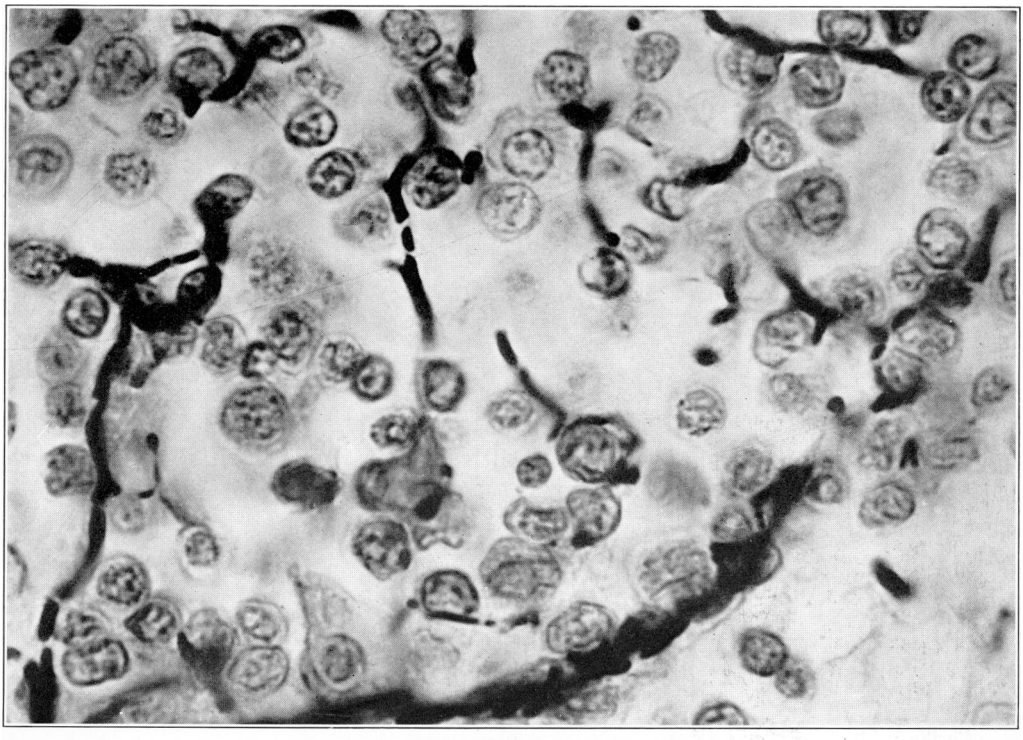

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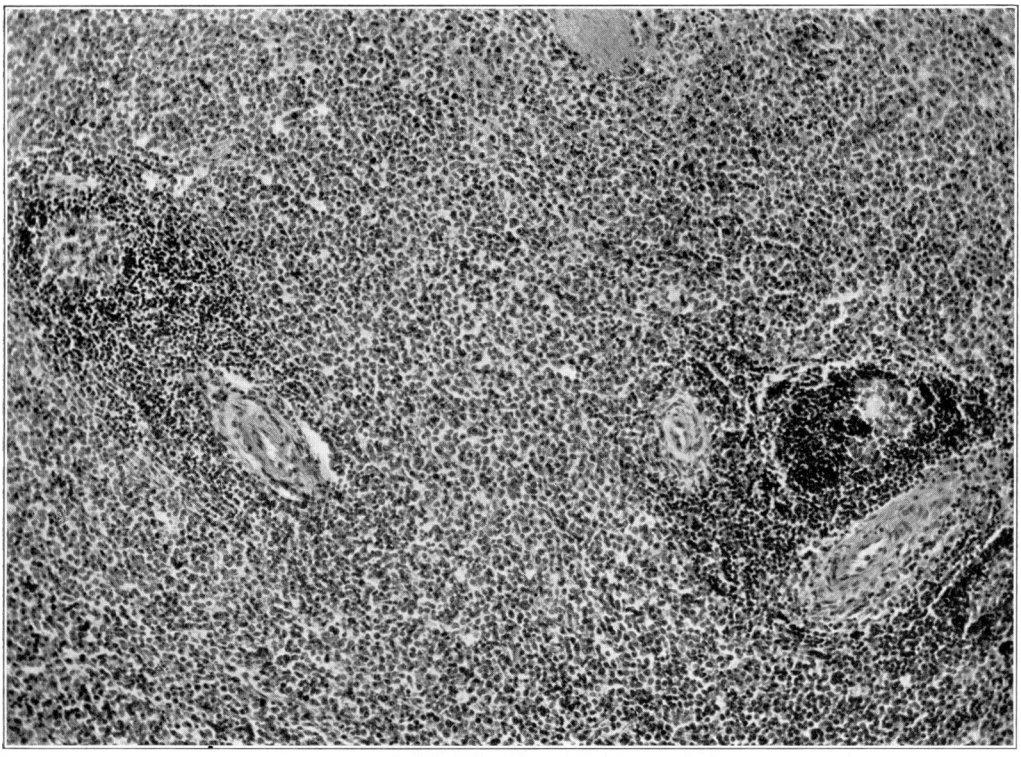
PLATE 112

FIG. 3. Spleen in myelogenous leukemia. Note the proliferation is between the nodules, which are somewhat atrophied. The change is in the red pulp, and differs distinctly from the change in lymphocytic proliferation in which the nodules are increased in size, encroaching on the red pulp.

FIG. 4. From a section of lymph node in erythrocytic leukemia to show typical megakaryocytes. Hematoxylin and eosin stain.



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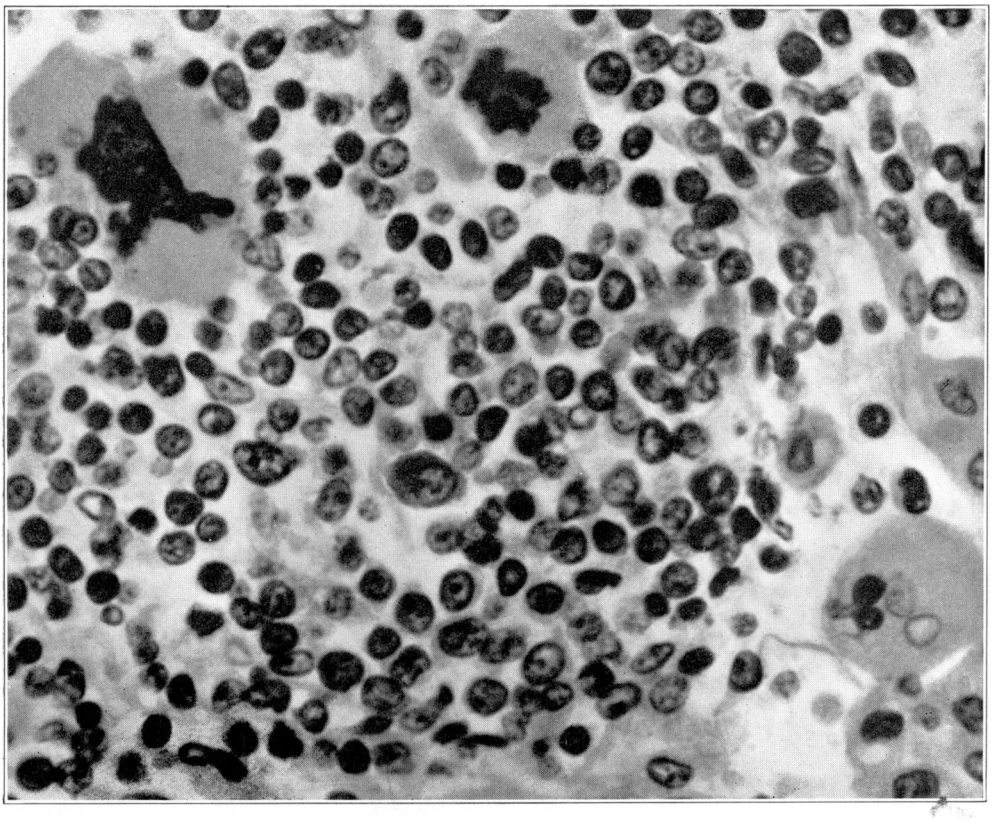

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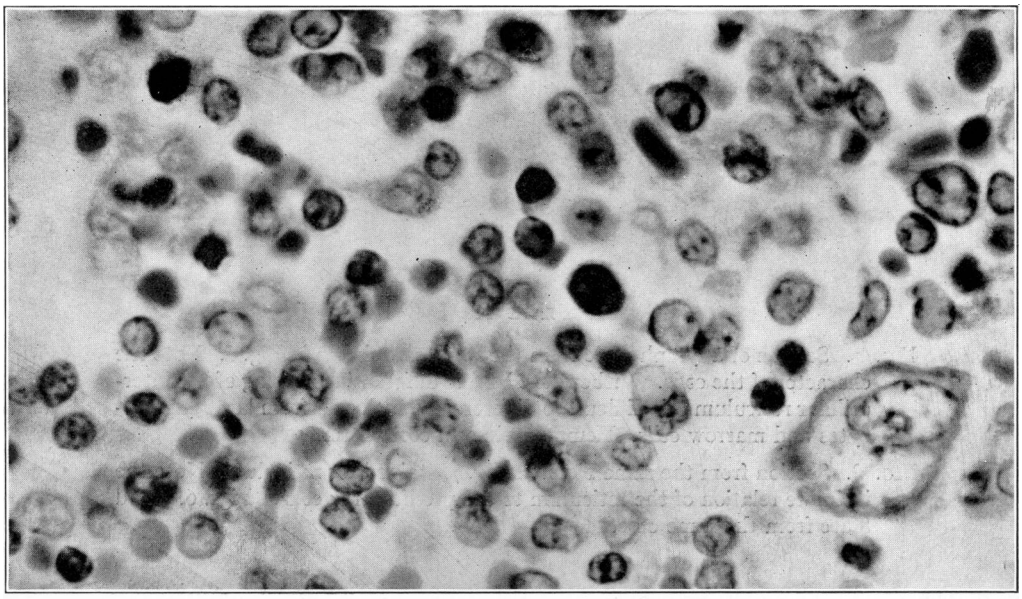
PLATE 113

FIG. 5. Section from the same node as Fig. 4. A young megakaryocyte is seen in the lower right hand corner. The pyknotic cells are "blasts." Note a diffuse infiltration of red blood corpuscles, a picture suggesting that these have been formed locally.

FIG. 6. Lymph node in monocytic leukemia stained for reticulum. Note the characteristic reticulum in close contact with the proliferating cells. Note also that the proliferation is between nodules or around them. This nodule is decreased in size and is invaded to a slight extent at the periphery by the proliferating cells and the reticulum they produce.



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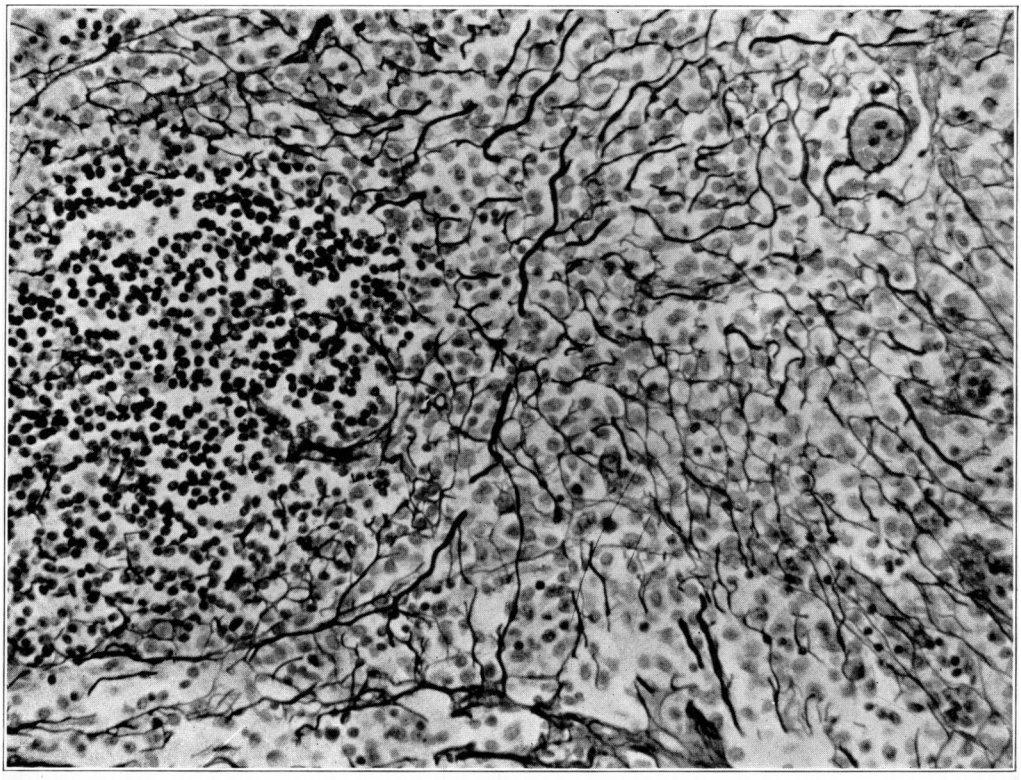

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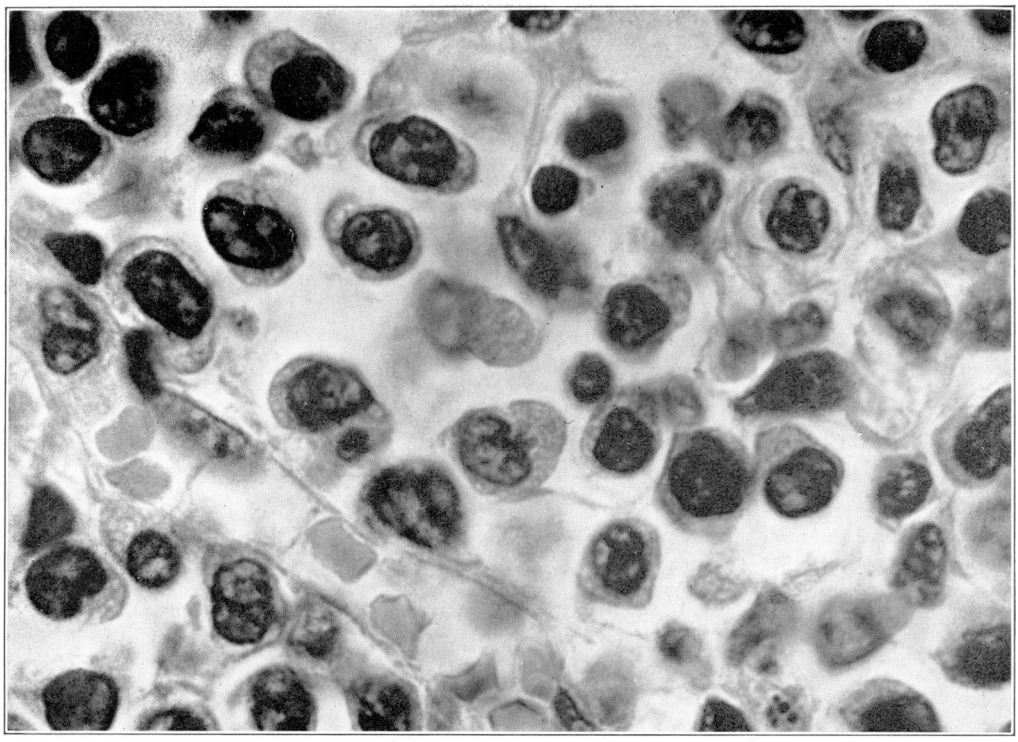
PLATE 114

FIG. 7. Section of a lymph node from the same case shown in Fig. 6. Note the character of the cells. Without the help of differential staining of the intercellular reticulum it is difficult to differentiate such cells from large lymphocytes and marrow cells. Hematoxylin and eosin stain.

FIG. 8. Section from the same block as Fig. 7, stained for reticulum. Note the intimate relation of the reticulum to the proliferating cells. Figs. 6, 7 and 8 are from the same case.



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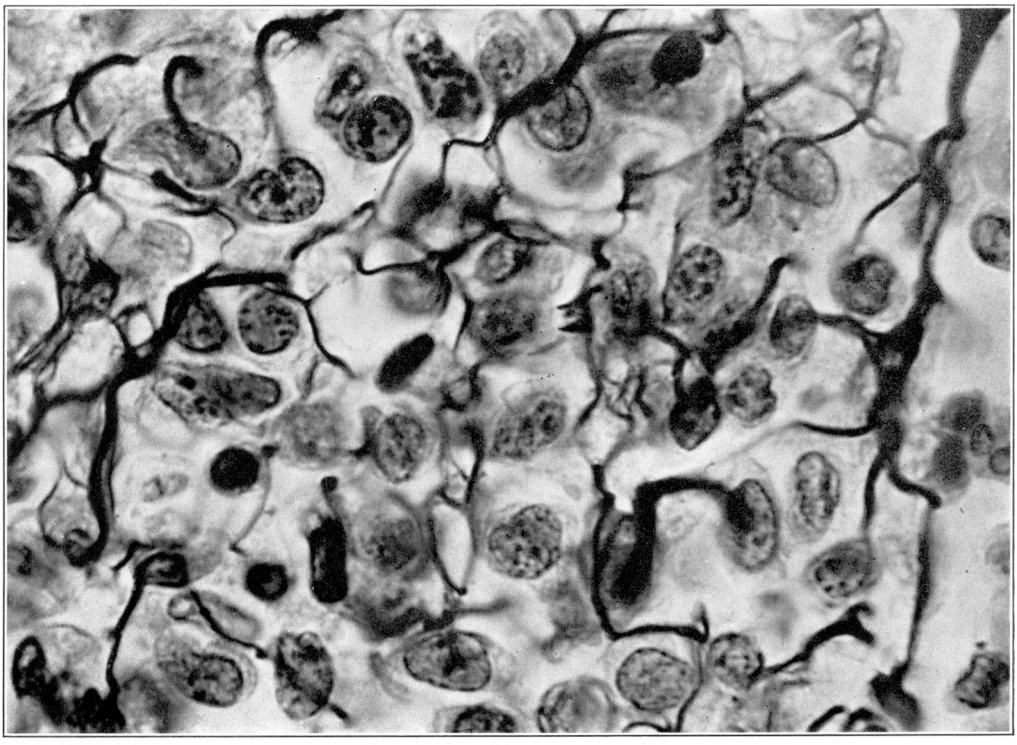

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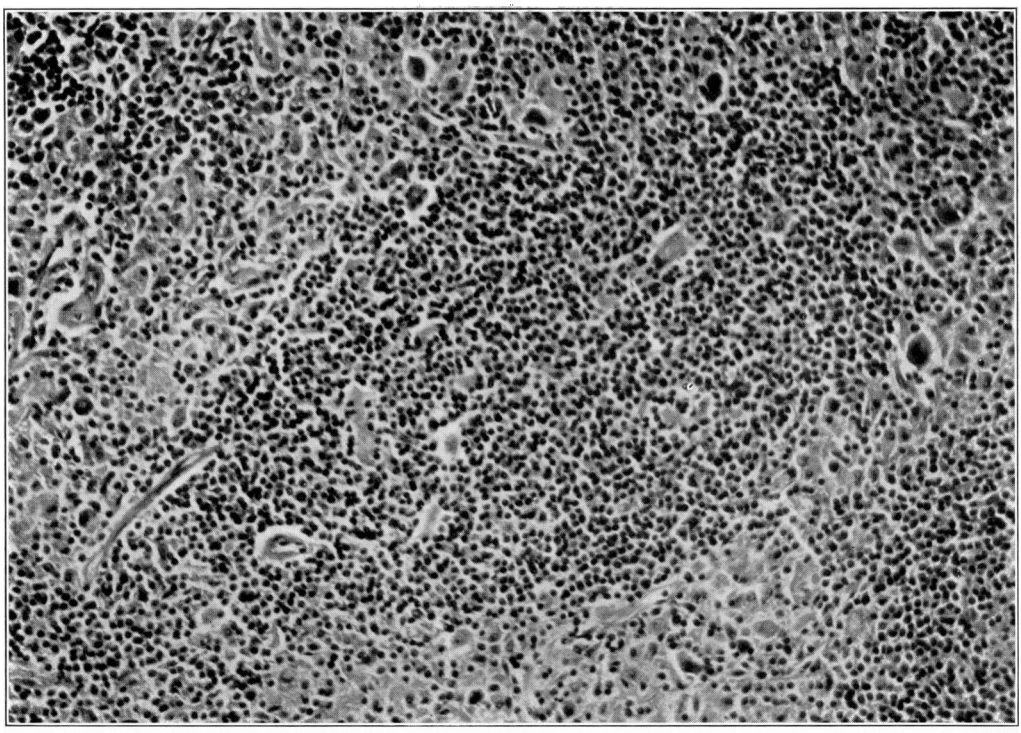
PLATE 115

FIG. 9. Spleen of Hodgkin's disease, reactive type. Note that the reticulum cell proliferation surrounds the malpighian nodule and has not involved the central part of the nodule. The nodules in this case were somewhat enlarged, as is frequently the picture at the beginning of the reaction. The decrease in nodule size appears to be due to the gradual encroachment of the process on the nodules, both in lymph nodes and in spleen, but the process starts as an extranodular reaction.

FIG. 10. Reticulum stain of a lymph node in the reactive type of Hodgkin's disease. Note the dense reticulum on the outside of the nodule shown in the upper and right hand portions of the photograph. The central and left hand portions are a part of a primary nodule, which at this time had become considerably infiltrated by the proliferating reticulum cells.



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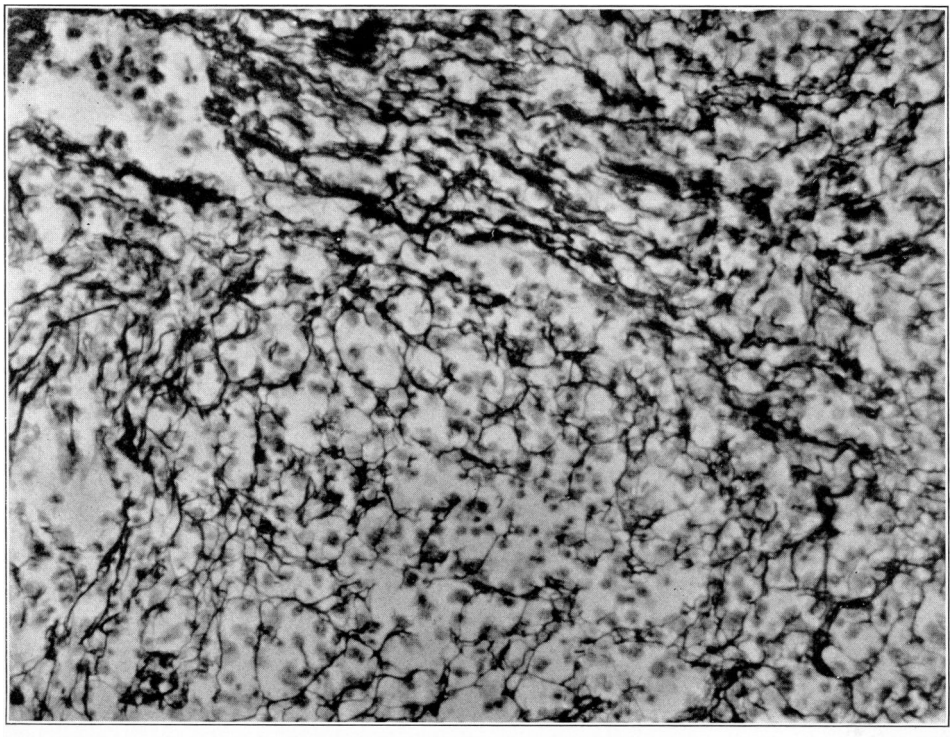

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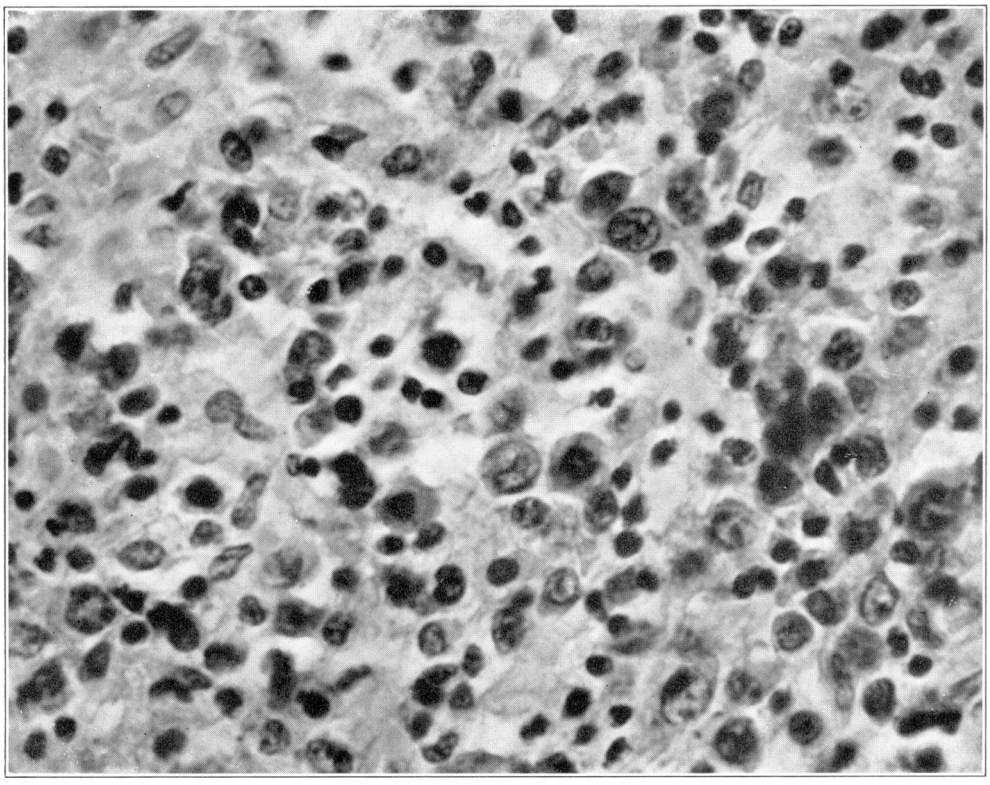
Plate 116

Fig. 11. Section of a generalized Hodgkin's process. This is from a lymph node and shows the pleomorphic character of the process. Hematoxylin and eosin stain.

Fig. 12. Reticulum stain of a section from the same block as Fig. 11. This shows the characteristic reticulum of the diffuse Hodgkin's process and demonstrates the fact that it is a hyperplasia of reticulum cells.



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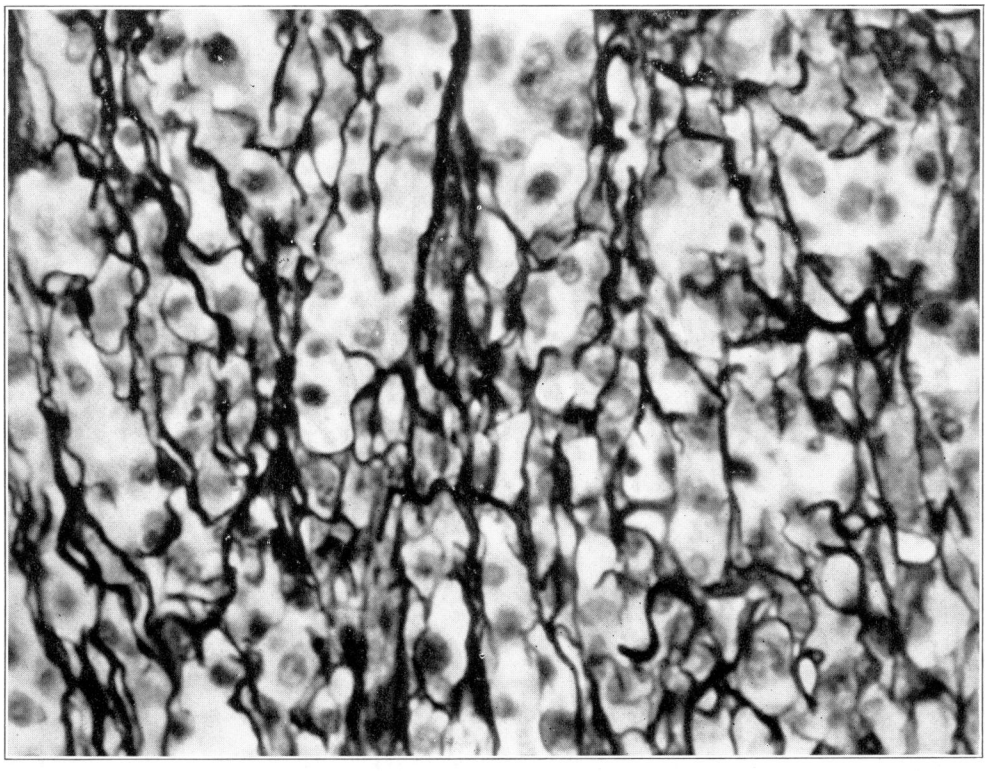

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