AN INTERPRETATION OF THE NATURE OF HODGKIN'S DISEASE *

E. M. MEDLAR, M.D.

(From the Hegeman Memorial Research Laboratory of the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, N. Y.)

The number of contributions relative to Hodgkin's disease is so large that it is impossible to present adequately the views of the various authors in a single article, unless the paper be devoted entirely to that phase of the subject. The review of Simonds [1] renders another article on this topic superfluous at the present time, for little has been added in the way of further clarification of this disease since his article was published. Our references to the literature will, therefore, be confined to citing certain points of view pertinent to the discussion of Hodgkin's disease we desire to present.

It is generally conceded that there is a pathological and clinical entity which justifies the grouping of certain cases under the term "Hodgkin's disease." The features which allow such a separation are so well known that no comment is necessary.

The nature of Hodgkin's disease is still very uncertain. There are two schools extant at present. The one school maintains that the disease is neoplastic in nature. The adherents to this view maintain that the tumor is primary in the lymphoid tissues of the body.

The second school believes that Hodgkin's disease is of an infectious nature. Bacteriological studies by different investigators have led to no single microörganism as the etiological agent. The tubercle bacillus has been held to be the inciting agent by some authors. The reason for this deduction has been the obtaining of tubercle bacilli from Hodgkin's tissues. The irregularity of these findings has led to a belief that to obtain Hodgkin's lesions it is necessary to have a certain type of tubercle bacillus which has a certain degree of pathogenicity. More recently L'Esperance [2] has presented evidence which suggests that the avian tubercle bacillus might be the etiological factor.

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Other investigators, Bunting and Yates,[3] have failed to find the tubercle bacillus frequently in Hodgkin's lesions, but have found diphtheroid organisms quite consistently. More recently, Haythorn[4] has obtained a culture of monilia from the tissues of a case of Hodgkin's disease.

In the study of tuberculous lesions in experimental animals we have noted the occurrence of numerous giant cells in lungs, liver, spleen and lymph nodes which we were unable to differentiate from the giant cells seen in Hodgkin's lesions. We observed these lesions suggestive of Hodgkin's disease first in rabbits inoculated with virulent avian tubercle bacilli. Upon further study we found similar lesions in guinea pigs, rabbits and calves infected with virulent bovine tubercle bacilli. We have also observed similar lesions in guinea pig and human tissues infected with virulent human type tubercle bacilli.

A thorough study of the various tissues of the experimental animals and of human tuberculous tissue led us to the conclusion that the cells which resembled the Sternberg giant cells of Hodgkin's lesions were megakaryocytes. At certain stages of acute tuberculosis there was a marked hyperplasia of the megakaryocytes in the marrow, with a wandering-out of these cells from the marrow into the circulation and thence into the various tissues involved in the tuberculous process. We have not observed this phenomenon in chronic tuberculosis, although it is possible that it exists to a slight degree.

The marked hyperplasia of the megakaryocytes in acute tuberculosis and our inability to distinguish between the megakaryocytes in the tissues and the Sternberg giant cells in Hodgkin's lesions led us to a study of the histopathology of Hodgkin's disease, with the possibility that the megakaryocyte might be the cell type primarily involved in the pathological process.

The material which we were enabled to study consisted of twenty-two autopsies and about one hundred surgical specimens.* Unfortunately the number of bone marrow specimens which we examined were very few. Of the twenty-two autopsies, bone marrow sections were available in but six instances. In four instances femur marrow

* We wish to express our appreciation for the kind permission of Drs. F. B. Mallory and F. Parker, Jr., to utilize the autopsy material and surgical specimens of Hodgkin's disease from the pathological laboratory of the Boston City Hospital. They granted the study of the skin nodule from a case of myelogenous leukemia also.

alone had been procured and in two instances vertebral and femur marrow had been obtained at the time of autopsy.

During this study we were privileged to examine a biopsy specimen from the skin of an individual who had the clinical and blood picture of myelogenous leukemia. This individual had numerous nodules in the skin in various parts of the body. The study of the sections from this skin nodule gave the point of departure for the interpretation of Hodgkin's disease which will be presented here.

The histopathological picture present in sections of the skin nodule was complex. In places there were groups of nondescript cells (Fig. 1). These cells were round, with a round to oval nucleus and slightly granular cytoplasm. They might be called large lymphoid cells, reticular cells or simply non-differentiated cells. They probably are the parent or "stem" cell of the other cell types noted in the section. In other areas of a single section the following cells were noted in groups: neutrophilic leukocytes (Fig. 2), eosinophilic leukocytes, megakaryocytes (Fig. 3) and nucleated red blood cells (Fig. 4). In other areas these were found comingled.

From this study we considered that the lesion was the result of the differentiation of the multipotential parent cell of the marrow into the various cell types which it produced normally. In other words there were leukopoietic, erythrogenic and megakaryogenic centers all present in the skin because of the differentiation of a common parent cell into these various cell types.

Since we were interested primarily in determining the possible relationship of Hodgkin's disease to the megakaryocyte, our chief interest centered on the bone marrow. Our findings in this tissue will be given in detail since we believe that the pathology which we observed is of real significance. In brief, it may be stated that the bone marrow in every case in which we studied this tissue was pathological. We will limit our description of the histopathology to one section of vertebral bone marrow, since all of the other sections of marrow gave the same picture to a greater or lesser degree.

In our study of the marrow reaction in experimental tuberculosis in animals we traced the megakaryocyte back to a cell somewhat larger than a myelocyte. This cell has very little cytoplasm and a relatively large, deeply staining nucleus. The cytoplasm was often very granular. Since this cell appeared to be the premegakaryocyte

in animal marrow we naturally sought for the same cell type in the Hodgkin's marrow.

Fig. 5 shows the appearance of a considerable part of a section of vertebral marrow from a case of Hodgkin's disease without evidence of tuberculosis or of other infectious lesions. Note the considerable number of nondescript cells which resemble the cells shown in Fig. 1. Whether these are premegakaryocytes or "stem" cells, one cannot say with certainty. One may state, however, that here is present a hyperplastic marrow with undifferentiated cells predominant. No megakaryocytes are seen.

Fig. 6 gives a picture also commonly met with in this same section. Here are shown two groups of the immature cells and no megakaryocytes in the field.

Fig. 7 shows an area a short distance from Fig. 6. Note the three megakaryocytes of different size and different nuclear appearance. Note also the group of cells similar to those in Fig. 6 just above the smallest megakaryocyte.

Fig. 8 is a portion of bone marrow in the same part of the section as Fig. 6. Here are shown five megakaryocytes and no groups of cells as shown in Fig. 6.

Figs. 9, 10 and 11 are higher magnifications from the same general area as Figs. 6, 7 and 8, to show that in all probability the typical megakaryocyte is the result of fusion of several of the smaller cells. Note that in Fig. 10 the complicated nuclear structure is quite similar to that in Fig. 11. There is, however, no abundant and definite cell cytoplasm as in Fig. 11. Note also the distinct granular cytoplasm in all three figures. This is more clearly seen in Fig. 11.

Fig. 12 shows an area of fibrosis in the same section from which the above photomicrographs were taken. In this particular field there are no tumor cells. The tissue is made up entirely of fibroblasts and lymphocytes. This corresponds to the fibrotic areas commonly found in Hodgkin's lymph nodes.

Fig. 13 is from another part of the same section of vertebral marrow and shows the picture commonly seen in scirrhotic Hodgkin's lymph nodes. Note the ameboid shape of the Sternberg giant cell in the center.

From the above description it will be seen that all of the complex picture of Hodgkin's disease can be demonstrated in a single section of bone marrow. The points we wish to emphasize are (1) hyper-

plasia of the marrow with a marked increase of immature cells which probably are the progenitors of megakaryocytes; and (2) presumptive evidence that the giant cells (megakaryocytes) are the end-result of fusion of several premegakaryocytes.

Mitotic figures were observed quite often in the hyperplastic marrow. The majority of mitotic figures were in the small parent cell. Occasionally one found a complex multiple mitotic figure in the large megakaryocyte. These observations also hold for the lesions found in other tissues in the body.

Since the Hodgkin's lesions, as seen in the various tissues of the body, differ in no essential respect from those described above in the bone marrow, further description would seem unnecessary. There is one point relative to the tumor cells that should be emphasized, and that is their ability to wander about in the tissues. This was shown to a striking degree in some of the surgical specimens which were promptly placed in Zenker's solution or in 10 per cent formalin.

Discussion

Any deliberation on diseases in which the blood-forming tissues of the body are chiefly concerned must necessarily be many-sided because of the complexity and the distribution of the tissue under consideration. We have observed but little in the pathology of Hodgkin's disease that has not been recorded in the literature already. The interpretation of the disease which we wish to present departs in certain respects from that presented in the literature. Our interpretation is given because to us it clarifies to some degree the nature of the disease. We are well aware of the fact that this interpretation departs rather radically from precedent and from authority. However, from the data we have at hand, our deductions appear logical to us. We do not believe that our views are final and we have no intention of being dogmatic in our statements.

The histopathology found in a nodule from the skin of an individual who had the clinical and hematological syndrome of myelogenous leukemia has a very important bearing on the interpretation of Hodgkin's disease given in this article. The ability to demonstrate in a single section of this nodule the various cell types, in groups as well as comingled, which are known to be produced in the bone marrow is, we believe, of great significance. It suggests that

all of these cell types have a common parent cell. Such a view is held by many authors, Bunting,[5] Maximow[6] and others. This leads one to a belief in the unitarian theory of hematopoiesis in the bone marrow. If, as we postulate, Hodgkin's disease may be a disease in which the megakaryocyte is the cell type chiefly involved, then it becomes apparent that Hodgkin's disease is closely related, genetically, to the myeloid leukemias and to the erythroblastic dyscrasias.

If one considers the derangements of hematopoiesis in the marrow from such an angle, then one recognizes that the further the process reverts to an embryonic state the greater will be the difficulty and the uncertainty of identification of the cells seen either in sections of tissue or in blood smears. It would seem probable that the parent cell of the megakaryocyte is a cell, which in its most immature state could not be successfully differentiated from a similar cell, which may be the parent cell of the erythrocyte or of the neutrophile. In other words, the more immature the cells of the marrow, the greater the uncertainty as to what type of cell they may become in their maturation. It is commonly known that in acute leukemic conditions it is, at times, extremely difficult, if not impossible, to determine with certainty whether the disease is of the myeloid or the lymphoid type. Some cases of Hodgkin's disease have been known to develop "lymphoid" leukemia. Since, to us, it appears that Hodgkin's disease is closely related genetically to the leukemias, it is not inconsistent that the leukemic manifestation should be an integral part of the disease process. From our study it would seem plausible that in this leukemic manifestation the cells may be very immature and in such a state they might be easily confused with immature parent cells of the lymphoid tissues. Until such time as the "stem" cell of the lymphoid tissue can be unqualifiedly distinguished from the "stem" cell of the marrow, it would seem that one is not justified in being dogmatic on the subject. In such cases of Hodgkin's disease as develop a leukemic blood pressure, we suggest a careful study of the cell types to establish, if possible, the origin of the lymphoid-like cells, and not remain content with saying they are of lymphoid origin simply because we know that the lymph nodes are very commonly involved in the disease.

The report of Minot[7] is of interest relative to the presence of megakaryocytes in the circulation in cases of myelogenous leukemia. His observation of immature megakaryocytes and of abnormal plate-

lets tends further to establish the unitarian theory of hematopoiesis in the bone marrow. The finding of nucleated red blood cells may be explained on the same basis. The presence of nucleated red blood cells and of myelocytes in the blood stream in Hodgkin's disease, and of abnormal platelets and of myelocytes in cases of grave erythroblastic derangements, all point toward the probability that there is a single parent cell for hematopoiesis in the marrow. This cell must be multipotential. The great variations which are manifested in dyscrasias of the bone marrow should logically lead to a study of the factors which determine the development of the marrow cells mainly along the line of neutrophiles in one case and along the line of erythrocytes in another, rather than to a superficial and artificial separation of these manifestations into distinct pathological or clinical entities.

While a classification of the pleomorphic derangements of hematopoiesis is necessary, such a classification, as far as the bone marrow is considered, should be used merely to indicate the predominant phase of a complex pathological process in which, fundamentally, a single type, multipotential cell is concerned.

Recent reports by Furth and Stubbs [8, 9] on leukosis in fowl bear directly on our discussion. They state that they have found two distinct types of disease, myelogenous and erythroblastic. A very significant feature of their findings is that when blood from the myelogenous type is injected into normal fowl, the disease reproduced is not uniform in type. Some of the fowl develop the myelogenous type, others show the erythroblastic type, while in still other fowl injected with blood from the same source a mixed type of disease becomes manifest. The same lack of uniform results occurs when blood from the erythroblastic type is injected into normal fowl. These observations point very strongly to a common multipotential parent cell for the complex disease process which they have found in the leukosis of fowl. It is of interest, also, that they have not noted the occurrence of typical lymphocytic leukemia in their studies. This would suggest that, in the fowl at least, there is a distinct difference between the leukemias of bone marrow origin and those of lymphoid tissue origin. There is a certain amount of evidence to suggest that there is also a distinct difference between these two types in the human being. That the most embryonic types of these diseases may closely resemble each other is probable.

Symmers[10] regards Hodgkin's disease as a systemic disease in which all of the hematopoietic tissues of the body are involved. He, as well as others, has noted the marked abnormality of the bone marrow. According to this author the disease is neither infectious nor neoplastic in nature. If one establishes too rigid a formula to which all malignancies must conform, then it would seem that no dyscrasia of the blood could be considered as a malignancy. There is no tissue in the body which is so pleomorphic or so mobile as the hematopoietic tissue. Therefore, in considering this tissue it would seem inconsistent to regard it in the same way as one would the epidermis. In a malignancy of the epidermis the essential considerations are (1) the autonomy of the newgrowth, and (2) the surety of the production of epidermal cells wherever the autonomatous cells may metastasize. These criteria are present in the leukemias, erythroblastic dyscrasias and Hodgkin's disease, if one considers primarily the characteristics of the parental cell of the bone marrow. The varied cellularity of these diseases would seem to be due to the fact that the parental cell is multipotential instead of unipotential as in the case of an epithelioma.

With the above discussion in mind one may logically construct the following schematic outline of hematopoiesis.

This schematic representation includes all that is, at present, accepted facts relative to hematopoiesis and ideas which, at present, are plausible although not proved. While there are controversial points in the concept, still it gives a workable, logical formula which enables one to understand more lucidly the various manifestations one observes in abnormal hematopoietic tissues and circulating blood. A recognized controversial point, to mention but one, is the placing of the monocyte as arising from the lymphoblast. Some authors hold that this cell arises from fixed connective tissue phagocytes, while others maintain that it is of bone marrow origin. Certain observations of the author (unpublished) lead him to believe that the lymphoid tissue (including the spleen) is the seat of origin of the monocyte. In an unsolved question such as this, one must admit the possibility that any point of view may be correct until unquestionable proof is established of the exact origin of the cell. Too much reliance must not be placed, however, upon a positive oxidase reaction or a certain arrangement of supravitally staining granules, for the parental cell may not show these characteristics.

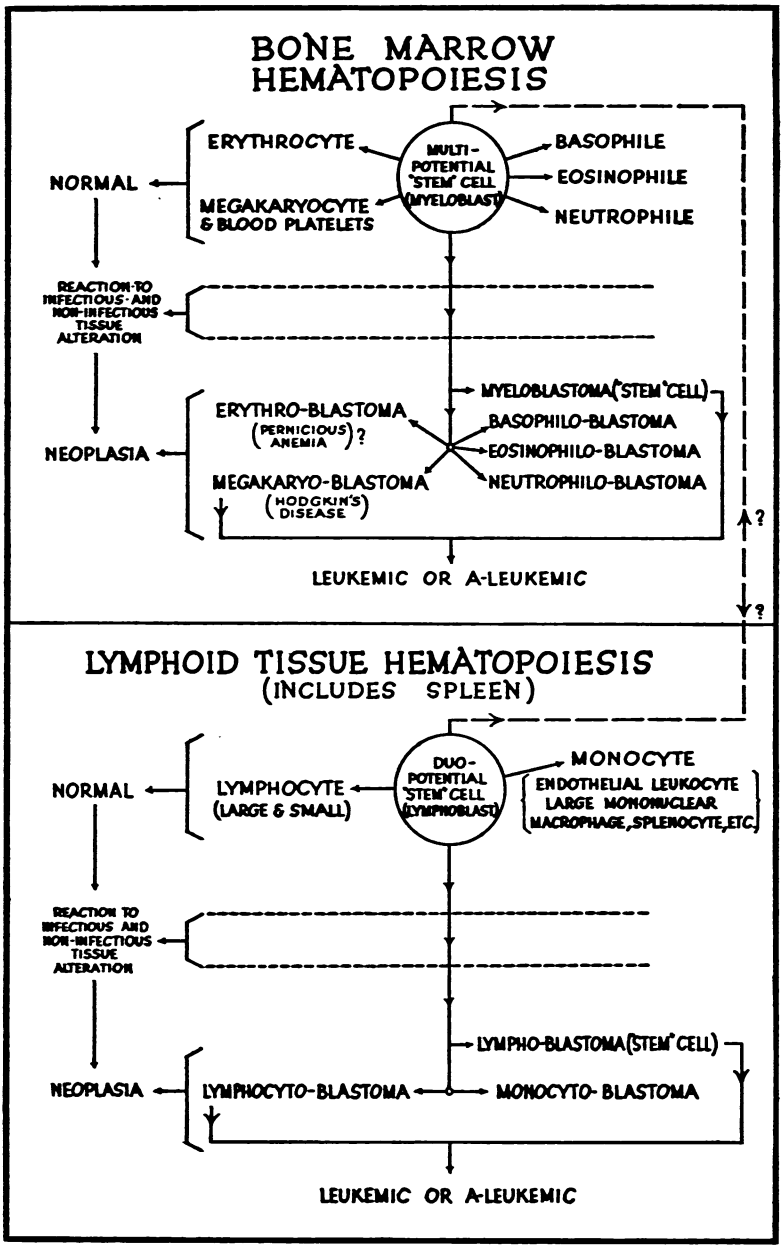

BONE MARROW
HEMATOPOIESIS
NORMAL
ERYTHROCYTE
MEGAKARYOCYTE & BLOOD PLATELETS
MULTI-POTENTIAL "STEM" CELL (MYELOBLAST)
BASOPHILE
EOSINOPHILE
NEUTROPHILE
REACTION TO INFECTIOUS AND NON-INFECTIOUS TISSUE ALTERATION
NEOPLASIA
MYELOBLASTOMA ("STEM" CELL)
ERYTHRO-BLASTOMA (PERNICIOUS ANEMIA)?
BASOPHILO-BLASTOMA
EOSINOPHILO-BLASTOMA
NEUTROPHILO-BLASTOMA
MEGAKARYO-BLASTOMA (HODGKIN'S DISEASE)
?
LEUKEMIC OR A-LEUKEMIC
?
LYMPHOID TISSUE HEMATOPOIESIS
(INCLUDES SPLEEN)
NORMAL
LYMPHOCYTE (LARGE & SMALL)
DUO-POTENTIAL "STEM" CELL (LYMPHOBLAST)
MONOCYTE
ENDOTHELIAL LEUKOCYTE
LARGE MONONUCLEAR MACROPHAGE, SPLENOCYTE, ETC.
REACTION TO INFECTIOUS AND NON-INFECTIOUS TISSUE ALTERATION
NEOPLASIA
LYMPHO-BLASTOMA ("STEM" CELL)
LYMPHOCYTO-BLASTOMA
MONOCYTO-BLASTOMA
LEUKEMIC OR A-LEUKEMIC

Chart 1

It will be noted that in the schematic outline under consideration a line has been drawn from the "stem" cell of the marrow to the "stem" cell of the lymphoid tissue with arrows pointing in either direction. This line is to suggest that there may be a possibility of the myeloblast assuming the function of the lymphoblast, or *vice versa*. Whether this does actually occur in mature life would appear impossible to prove since, at present, no sure differentiation can be made between a "stem" cell of the lymphoid tissue and a similar cell of the bone marrow. If it is possible for these cells to assume functions foreign to their usual rôle, then one must admit the possibility of the abnormal cells in Hodgkin's lymph nodes being derived from lymphoblasts. However, such an occurrence appears remote to the author for one does not see erythrogenic or leukopoietic centers commonly in these lesions. It would seem illogical for the lymphoblast to take over but a small part of the function of the myeloblast.

In considering such an outline as given above one can conceive that the bone marrow response in a case of severe infection might become so abnormal that a neoplastic condition would be simulated. That such conditions do arise should not lead one to hypothecate that all blood dyscrasias are the result of infection and that there is no true non-infectious neoplasia of the hematopoietic tissues. Such reasoning applied to other tissues we know would lead to erroneous conclusions. For instance, over-production of connective tissue in tissue repair we know seldom ends in a true neoplasm, although the gross and microscopic appearance might closely simulate an early neoplasm. To conclude that neoplasms never arise during the course of tissue repair we know would be without foundation. Autonomy of cell growth is a fundamental essential for neoplastic development. To recognize such autonomy at its inception is, at present, impossible. This is just as true for the hematopoietic tissue as it is for the fixed connective tissue. Different degrees of malignancy are recognized in neoplasms. This is in all probability, as true for the hematopoietic tissues as for any other tissue. The majority of medical men admit that neoplasms of the skin, bone and other tissues arise without infections playing any rôle. We can see no logical reason why the same may not be true of the hematopoietic tissue.

Those who are of the opinion that Hodgkin's disease is infectious in nature also regard all of the leukemias as being caused by some

pathogenic microörganism. We believe that such an interpretation of these dyscrasias is due to the fact that leukocytic responses of all types have come to be regarded almost wholly as indicative of an infectious process. The significance of the response on the part of the blood cells as representing a broad biological response, common to both infectious and non-infectious tissue damage, seems to have received but little acclaim. It seems that we are more easily impressed by the activities of the pathogens than by the activities of the body tissues in their attempt to adjust themselves to a wide range of changing environments. At present the neutrophile is considered pathognomonic of an acute infection by the large majority of medical men. Since the parent cell of the neutrophile appears to be the same as the parent cell of the erythrocyte, it would appear unreasonable to pick out the neutrophile any more than the erythrocyte as pathognomonic of acute infection. Yet it is doubtful if anyone would look upon the presence of immature erythroyctes in the circulation as pathognomonic of acute infection. It would seem more logical to look upon all of the cells of the hematopoietic tissue as carrying on a definite physiological or metabolic function in the body, irrespective of the presence or absence of any infectious agent. One might say that the rôle of each leukocytic type is primarily to care for damage to the body tissues of one type or another, irrespective of whether this alteration is produced by a tubercle bacillus, a pneumococcus, necrotic tumor tissues, croton oil or sterile normal salt solution. Undoubtedly the determination of the definite function of each leukocytic type far antedates the presence of any pathogenic bacterium in the tissues. Logic suggests an interpretation of the response of the marrow and lymphoid cells upon the basis of the type of alteration in the body to which they respond, rather than upon the presence or absence of infection. One grants that infectious agents damage tissue, but so will boiling water. In either instance the leukocytic response will tell with considerable accuracy the degree and type of damage the tissues have sustained. If one is willing to regard the response on the part of the hematopoietic tissue in such a light, then it becomes evident that the leukemias of one type or another may properly be removed from the infectious diseases and placed logically under neoplasms.

Many observers, Bunting,[11] and others, have noted the marked increase of blood platelets and the presence of enormous blood platelets

in the circulating blood in Hodgkin's disease. Since Wright [12] has so clearly demonstrated that megakaryocytes are the cells from which platelets arise, the findings relative to the platelets in Hodgkin's disease fit in readily with the disease being primarily an involvement of the megakaryocyte.

The finding of increased or abnormal platelets is not peculiar to Hodgkin's disease. Such a phenomenon is also noted in acute lobar pneumonias, in acute tuberculosis and other acute processes. It would appear that blood platelets play a far more important rôle in the response to acute damage to tissues than is generally appreciated.

The finding of neutrophilic or eosinophilic infiltration in Hodgkin's lesions need not necessarily indicate the presence of an infectious agent. Their presence can just as logically be explained by the necrosis of the tumor cells.

Another common occurrence in Hodgkin's lesions is fibrosis. This occurs in bone marrow, as well as in lymph nodes and other tissues. From a purely theoretical consideration one may explain this fibrosis in the following way. If the tumor cell type is the megakaryocyte, then there will be a marked production of blood platelets in the tumor nodules. Blood platelets are closely connected with the formation of fibrin. Wherever there is much fibrin formation there is an organization of the fibrin by fibroblastic proliferation. This would lead to the marked fibrosis commonly seen in the more chronic Hodgkin's lesions.

By placing the primary lesion of Hodgkin's disease in the bone marrow one can more easily understand the irregular distribution of the lesions in the body. Lesions outside of the marrow may be considered metastatic tumor growths. These metastases, in all probability, take place through the blood stream. From a study of the circulating blood which we are pursuing at the present time, we have a certain amount of evidence that this is true. This study will be reported at a later date. Minot [7] has also noted immature megakaryocytes in the blood in Hodgkin's disease. Regarding the lymph node involvement as a metastasis through the circulation, one can understand the independent and spontaneous enlargement of lymph nodes, simultaneously or at different dates, in different parts of the body such as the groin and the axilla. Why the tumor finds lymphoid tissue especially suitable for metastatic growth remains at present an unsolved question. The same is true of the reason why

some lymph nodes or other tissues, such as the liver, are involved more frequently than others.

A study of the lymph node lesions gives evidence that the consecutive enlargement of lymph nodes in a certain area, such as the cervical nodes, is due to metastasis from one lymph node to its neighbor. One can quite frequently find numerous groups of the tumor cells within lymph ducts.

In lymph nodes, especially in early growth, one finds the tumor cells scattered in different parts of the organ with the architectural structure of the node fairly normal. Older lesions will show practically the whole of the node occupied by the tumor growth. If it is appreciated that the megakaryocyte can wander about in the tissues, then it is easy to understand the diffusion of the tumor throughout the node in the early stages.

Since megakaryocytes are commonly found in tissues in diseases other than Hodgkin's disease, diagnosis cannot be made by simply finding giant cells of the Sternberg type. Rather it is essential to have a pleomorphism of cells which represent the developmental cycle of the megakaryocyte. This pleomorphism ranges from the small parent cell to the typical megakaryocyte.

One finds in hyperplastic marrow in disease other than Hodgkin's the pleomorphism of cells representative of the developmental cycle of the megakaryocyte. This phenomenon, however, is much more prominent in the bone marrow of Hodgkin's disease than in other hyperplastic marrows. We have not found in tissues outside of the bone marrow the pleomorphism of cells representative of the developmental cycle of the megakaryocyte in diseases other than Hodgkin's disease or in certain cases of "stem" cell leukemia of the bone marrow. While neutrophilic and eosinophilic infiltration and fibrosis are commonly met with in Hodgkin's lesions, they need not be present. Their presence is not necessary to establish the diagnosis of Hodgkin's disease from a section of tissue.

The study of the developmental cycle of the megakaryocyte in the marrow in acute tuberculosis has led us to appreciate that megakaryocytes do not necessarily arise as such. One finds the small immature cell, which apparently is the forerunner of the typical megakaryocyte, and the next thing one observes readily in the hyperplastic marrow is the typical megakaryocyte. From a study of the marrow in Hodgkin's disease a certain amount of pre-

sumptive evidence is found which suggests that the small premegakaryocytes fuse to form the typical megakaryocyte. Such a finding allows an understanding of the difficulty in demonstrating various stages between the premegakaryocyte and the typical adult cell. It would seem logical to consider the premegakaryocyte or the immature megakaryocyte as analogous to the thrombocyte in the blood of birds and reptiles. Minot regards megakaryocytes with small nuclei as degenerative forms. From our observations the presence of several small nuclei in a megakaryocyte is not a criterion of degeneration of the cell.

From the above discussion it would seem as though Hodgkin's disease should be removed from the group of infectious diseases and placed as a malignancy of the hematopoietic tissues of the bone marrow. This also would imply the removal of this disease as a primary neoplasm of the lymphoid tissue. The involvement of tissues outside of the bone marrow could be logically regarded as metastatic growths.

A certain amount of evidence is presented which suggests that the cell primarily involved in the pathology of Hodgkin's disease is the megakaryocyte. To denote that the predominant phase of Hodgkin's disease, which distinguishes it from the other bone marrow dyscrasias, is the primary involvement of the megakaryocyte, the term "megakaryoblastoma" is suggested to designate real Hodgkin's disease.

Summary and Conclusions

1. Evidence is presented which suggests that Hodgkin's disease is a malignancy of the bone marrow. The type cell appears to be the megakaryocyte.

2. The developmental cycle of the megakaryocyte is presented. It would seem that the typical megakaryocyte is the result of fusion of several premegakaryocytes.

3. The histopathology of Hodgkin's disease is a pleomorphic aggregation of cells which represent the developmental cycle of the megakaryocyte. It is not essential to have fibrosis or eosinophilic or neutrophilic infiltration to establish the diagnosis of Hodgkin's disease.

4. The involvement of lymph nodes and other tissue outside of the bone marrow appears to be metastic tumor growth.

5. Evidence is presented which tends to prove that all blood cells arising from the marrow have a common parent cell.

6. The term "megakaryoblastoma" is suggested to designate true Hodgkin's disease.

REFERENCES

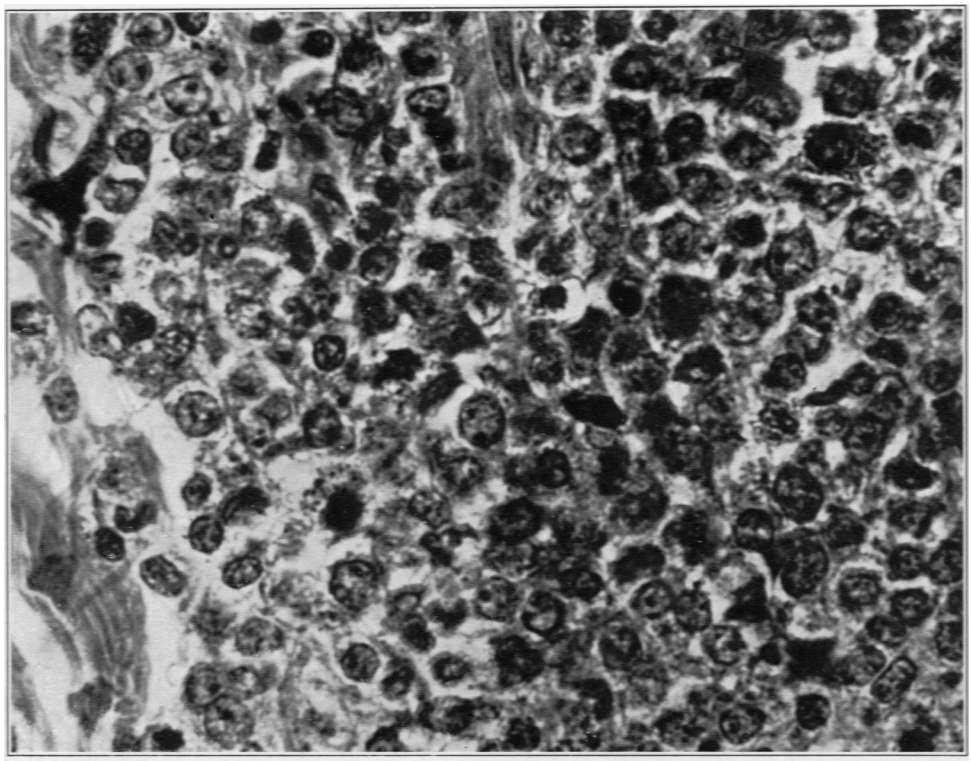
1. Simonds, J. P. *Arch. Path & Lab. Med.*, 1926, **1**, 394.
2. L'Esperance, E. S. *J. Immunol.*, 1930, **18**, 127.
3. Bunting, C. H., and Yates, J. L. *Arch. Int. Med.*, 1913, **12**, 236.
4. Haythorn, S. R. Personal Communication.
5. Bunting, C. H. *Physiol. Rev.*, 1922, **2**, 505.
6. Maximow, A. A. *Physiol. Rev.*, 1924, **4**, 533.
7. Minot, G. R. *J. Exper. Med.*, 1922, **36**, 1.
8. Furth, J. *J. Exper. Med.*, 1931, **53**, 243.
9. Stubbs, E. L., and Furth, J. *J. Exper. Med.*, 1931, **53**, 269.
10. Symmers, D. *Arch. Int. Med.*, 1917, **19**, 990.
11. Bunting, C. H. *Bull. Johns Hopkins Hosp.*, 1911, **22**, 114.
12. Wright, J. H. *J. Morphol.*, 1910, **21**, 263.

DESCRIPTION OF PLATES

PLATE 115

FIG. 1. Area of undifferentiated cells in a skin nodule from a case of myelo enous leukemia. × 800.

FIG. 2. Area of neutrophiles in same lesion as Fig. 1. Note a few eosinophil and a megakaryocyte in lower part of field. × 800.



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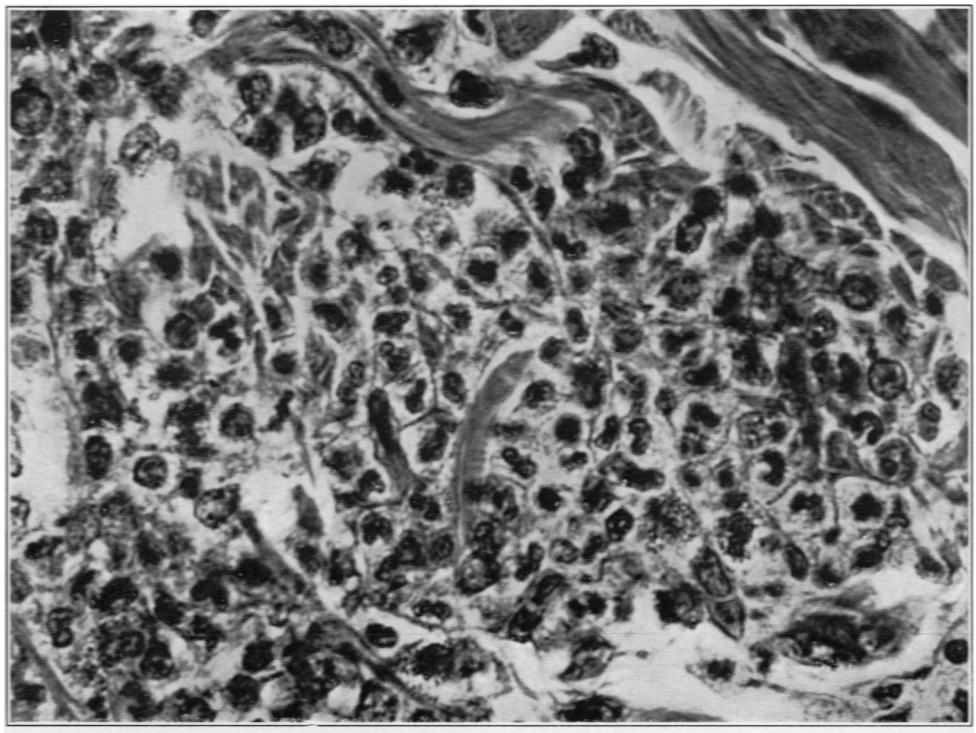

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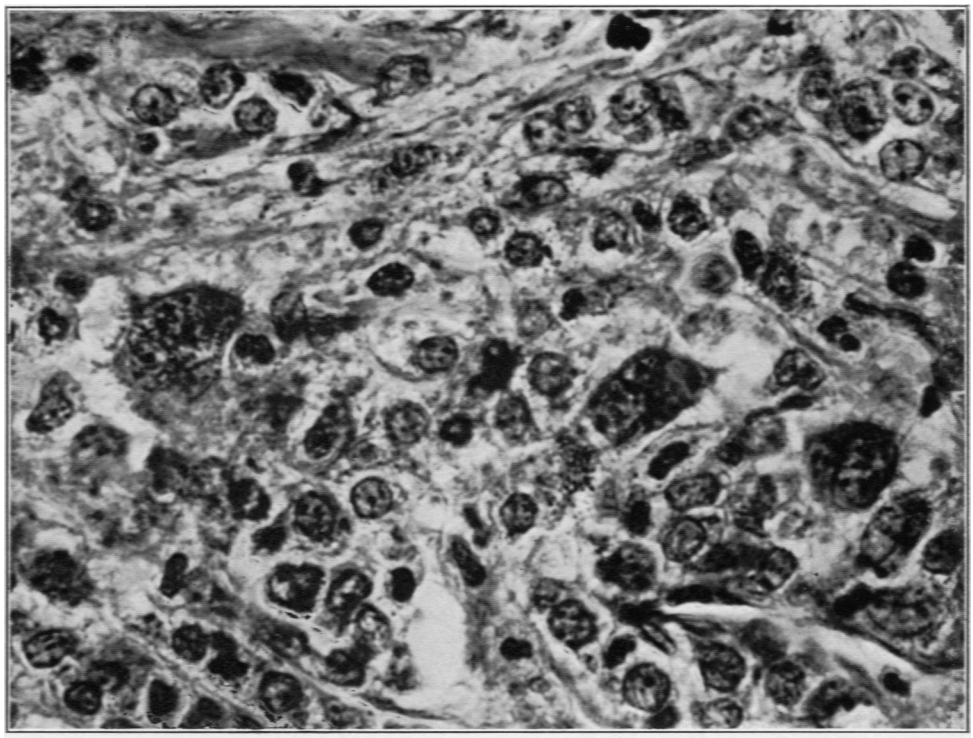
PLATE 116

FIG. 3. Megakaryocytes in same lesion as Fig. 1. Note eosinophile just below second megakaryocyte from right. Note also the numerous projections at the periphery of the megakaryocytes. × 800.

FIG. 4. Erythrogenic center in same lesion as Fig. 1. Note the nucleated red blood cells and the undifferentiated parent cells. × 800.



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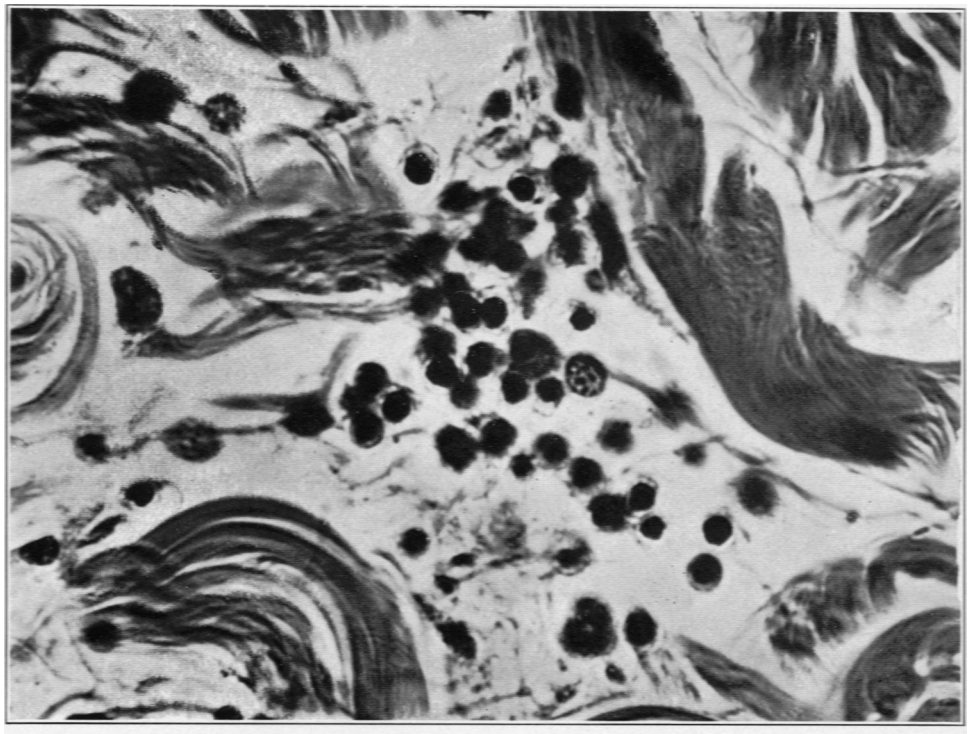

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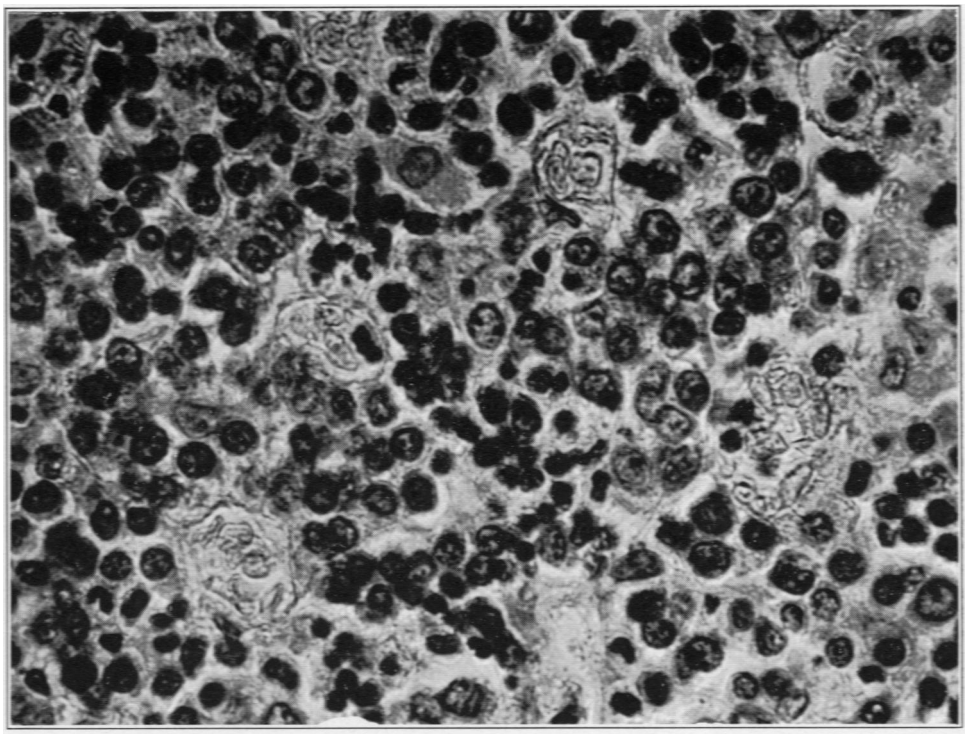
Plate 117

Figs. 5 to 13 are all from a single section of vertebral marrow from a case of Hodgkin's disease.

Fig. 5. Hyperplastic marrow showing undifferentiated cells, quite similar to those shown in Fig. 1, scattered throughout the field. No megakaryocytes present. × 800.

Fig. 6. Note two distinct, and one indistinct clump of undifferentiated cells in central portion of field. No megakaryocytes. × 800.



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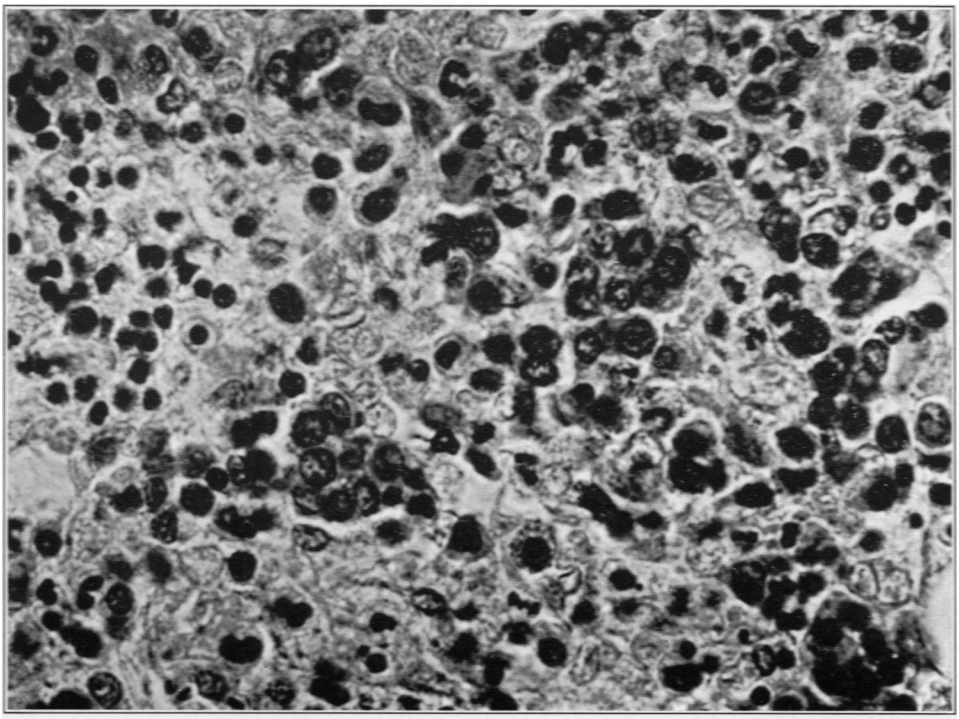

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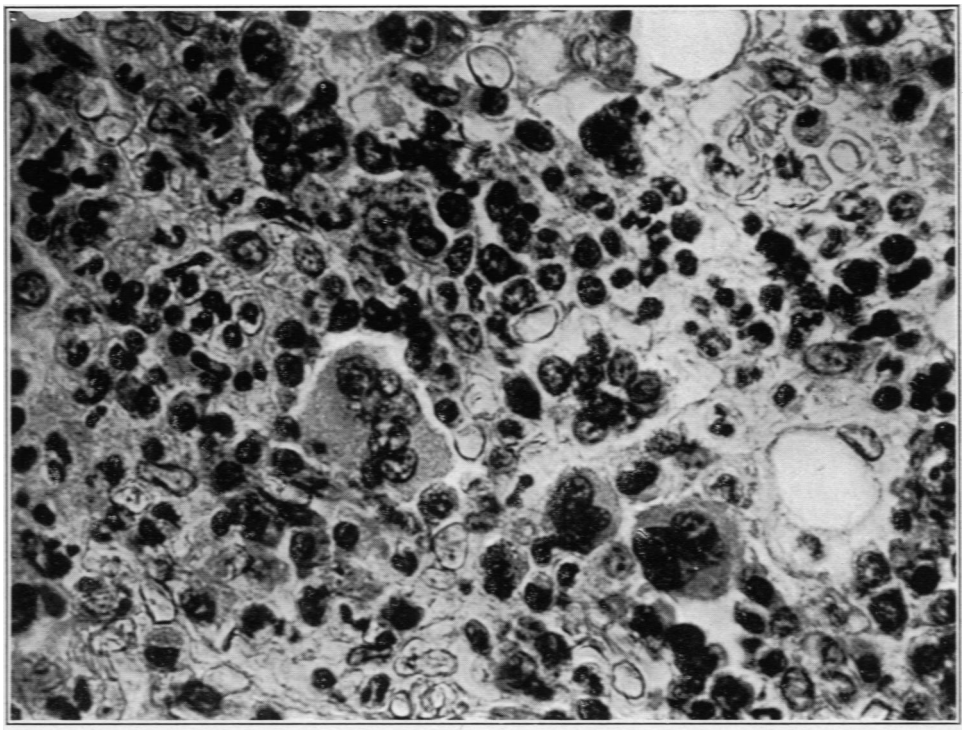
PLATE 118

FIG. 7. Three megakaryocytes and three clumps of cells in field. × 800.

FIG. 8. Six megakaryocytes in field. No clumps of cells. × 800.



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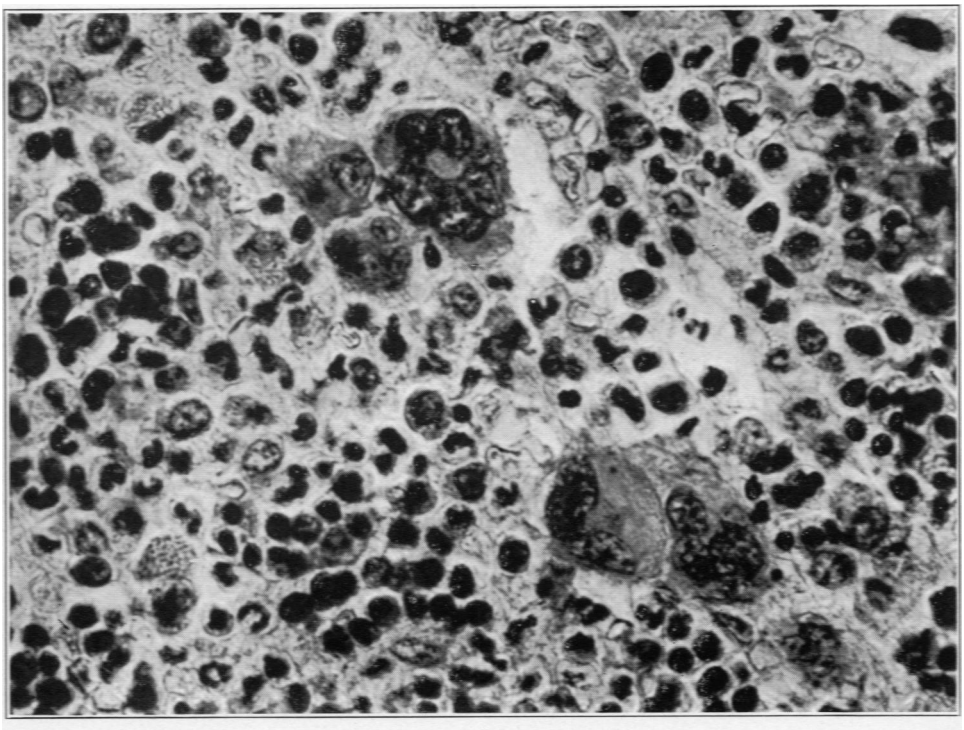
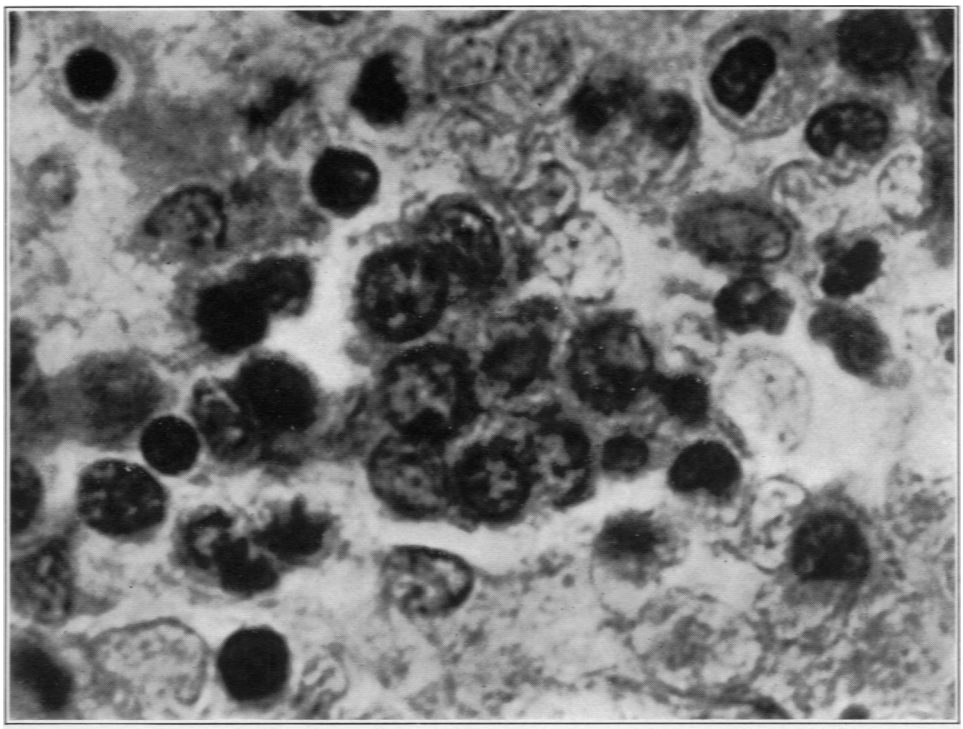


8

Plate 119

Fig. 9. Clump of cells in Fig. 6. Note granular cytoplasm and separate nuclei. × 1500.

Fig. 10. Note apparent fusion of nuclei giving nuclear structure quite similar to that in Fig. 11. Note granular cytoplasm. Note also that cytoplasm is much less than in Fig. 11. × 1500.



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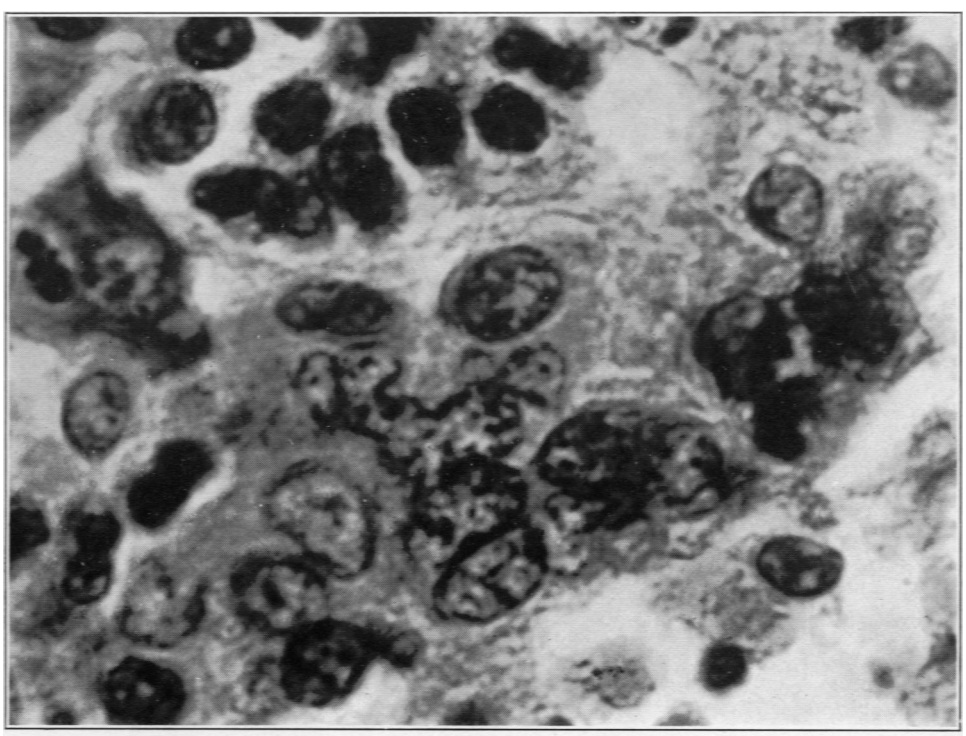

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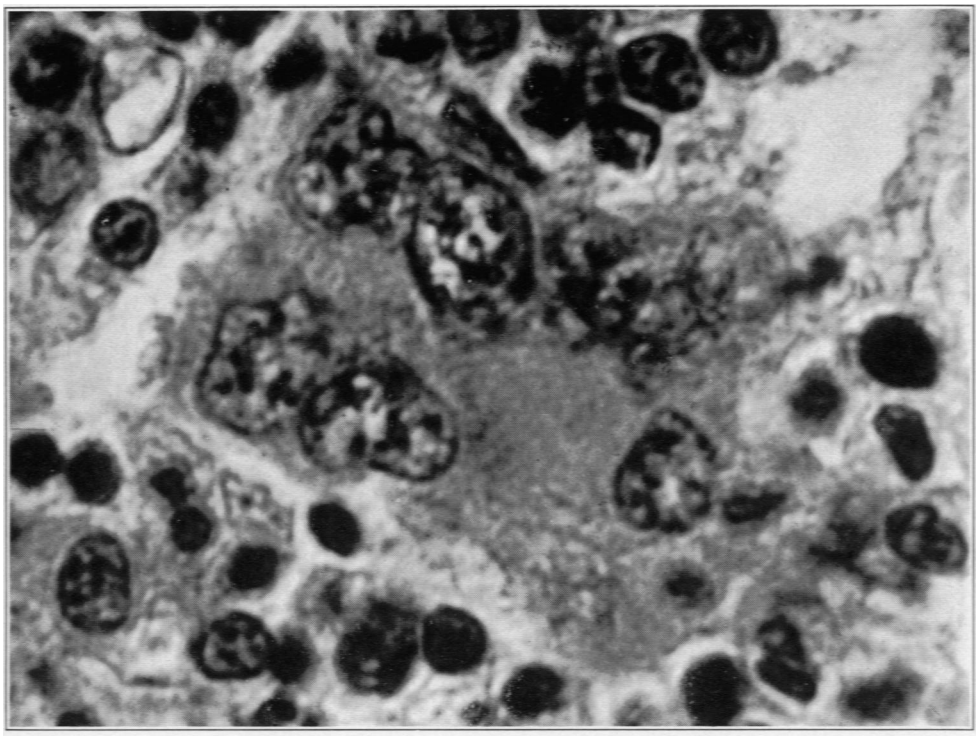
PLATE 120

FIG. 11. Megakaryocyte; nuclei are not all fused. Note abundant and granular cytoplasm. × 1500.

FIG. 12. Area of fibrosis; tissue composed entirely of fibroblasts and lymphocytes. × 500.



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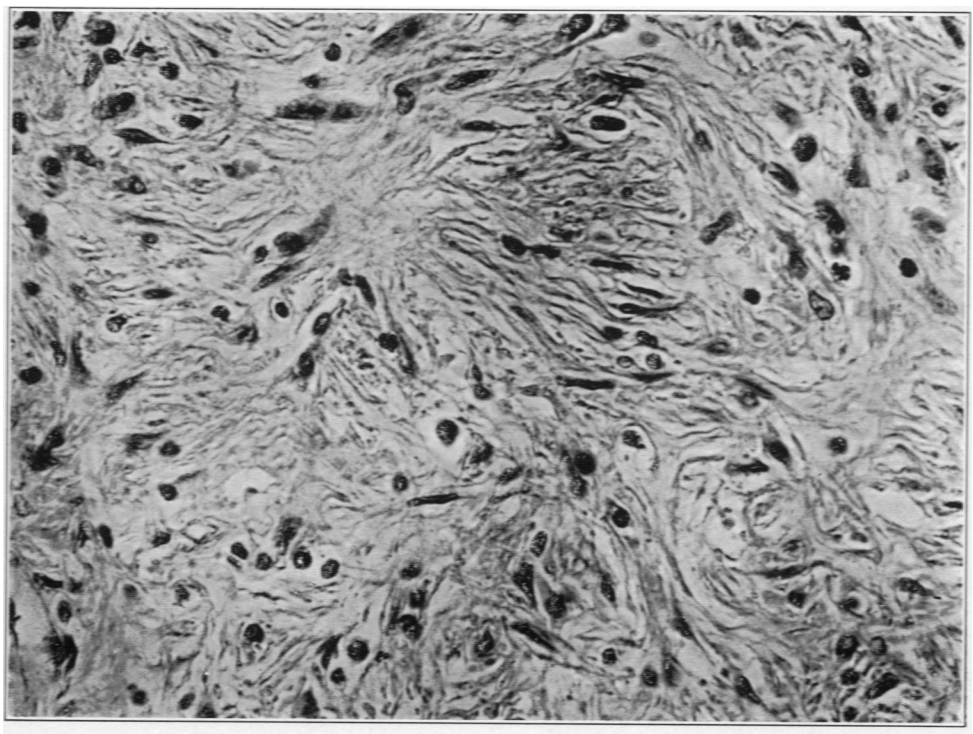

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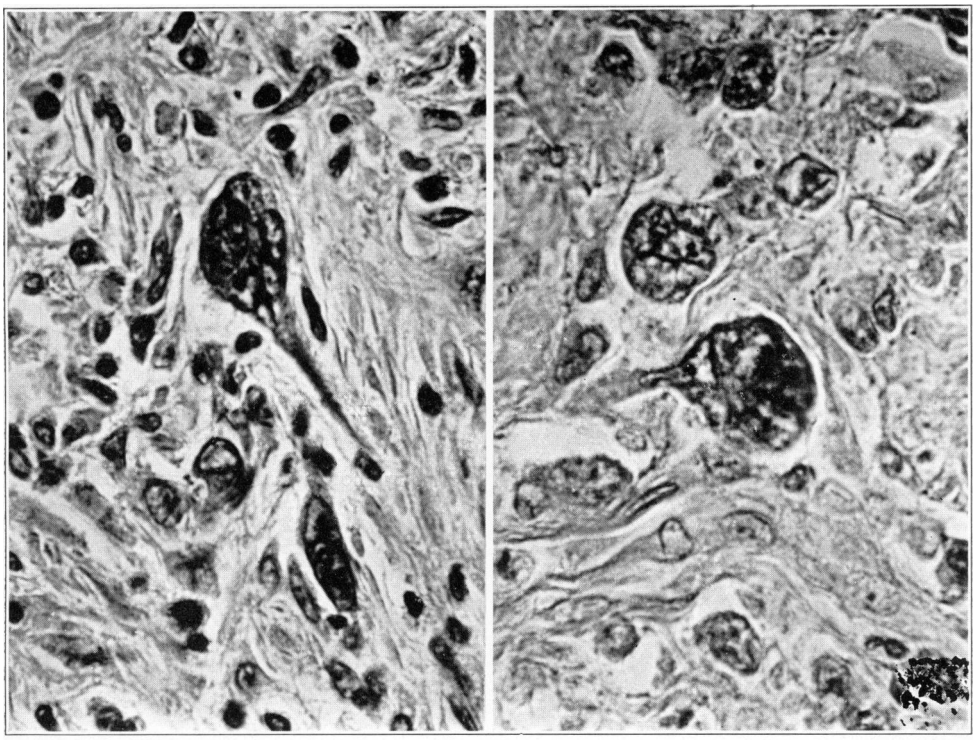
PLATE 121

FIG. 13. Typical scirrhous Hodgkin's lesion from same section as above photomicrographs. Note ameboid shape of giant cell in field. × 800.

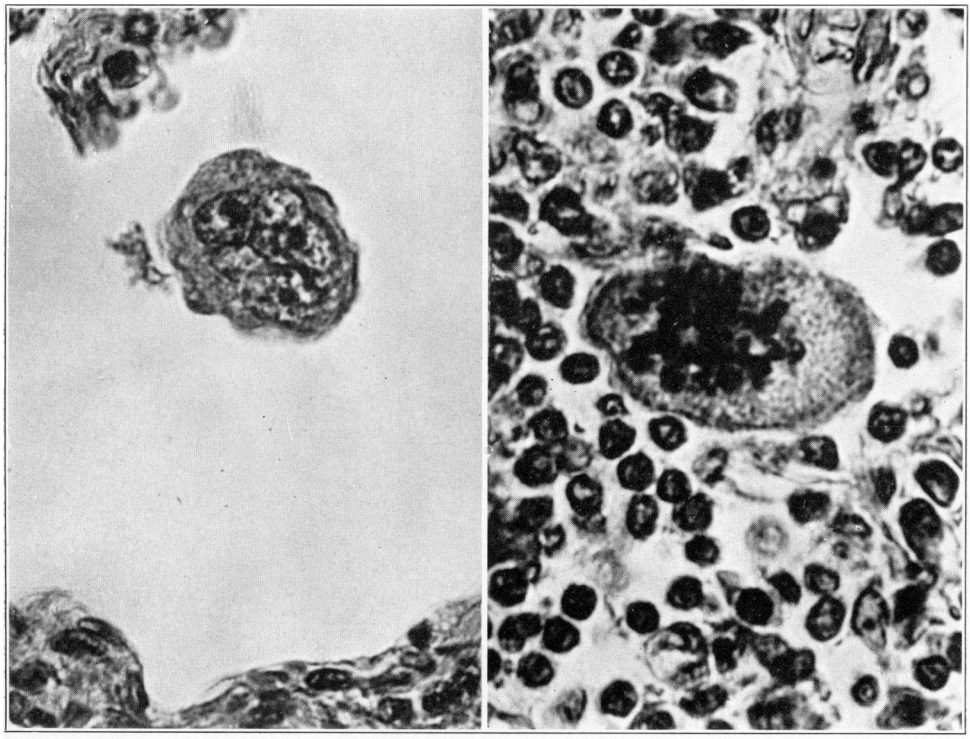
FIG. 14. Scirrhous Hodgkin's lesion in lymph nodes. Giant cells with pseudopod to left. × 800.

FIG. 15. Sternberg giant cell free within alveolar space of lung. × 800.

FIG. 16. Complex mitotic figure in Sternberg giant cell in lymph node. × 1000.



13 14



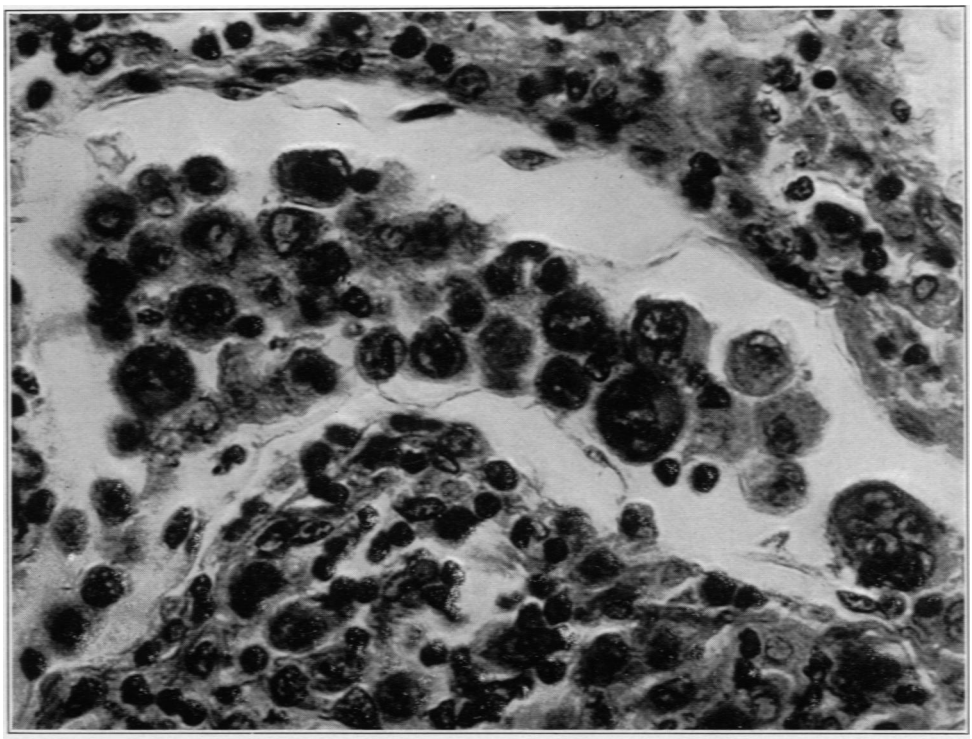
15 16

Medlar Nature of Hodgkin's Disease

PLATE 122

FIG. 17. Large lymph sinus in lymph node filled with Hodgkin's tumor cells. Note pleomorphism of cells. × 1000.

FIG. 18. Small area from same section as Fig. 17 showing a predominance of Sternberg giant cells. × 1000.



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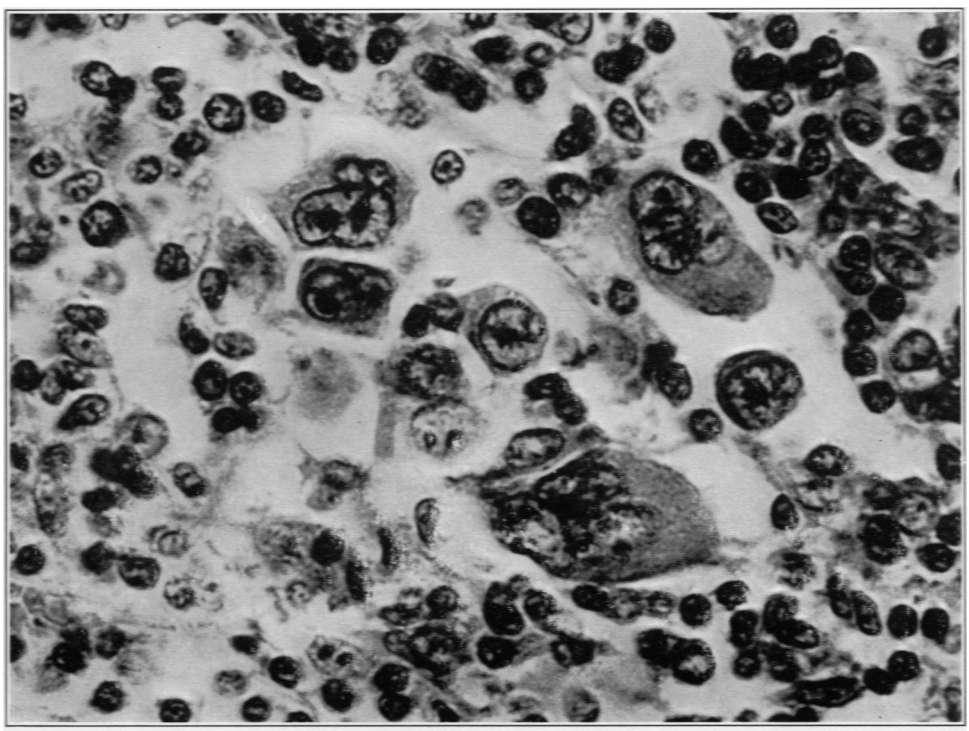

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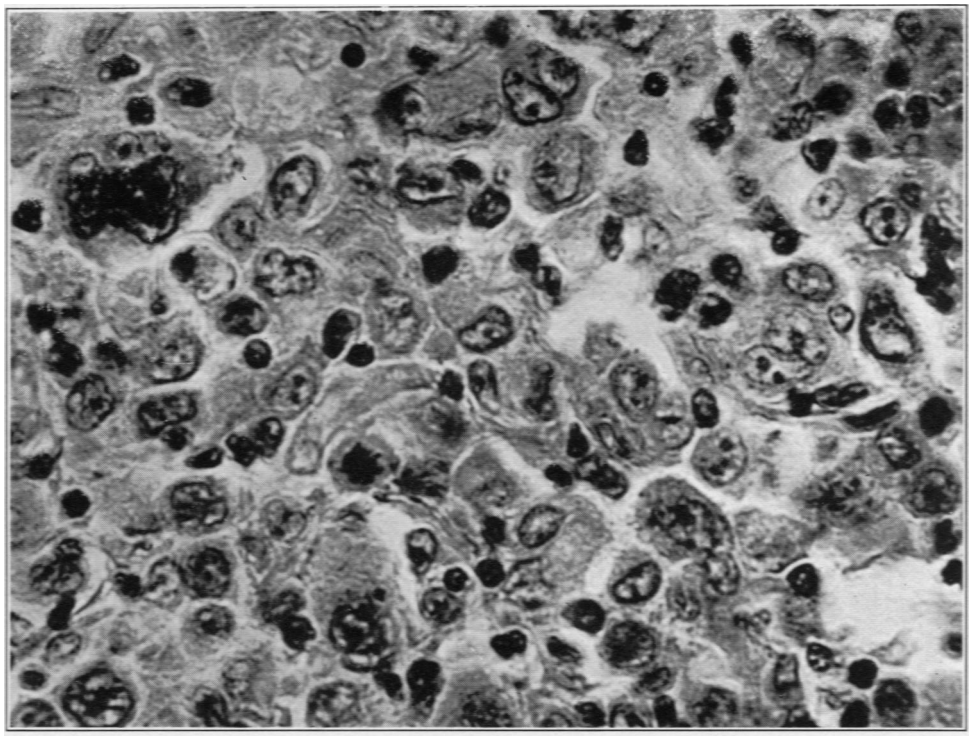
PLATE 123

FIG. 19. Typical morphology of tumor cells in Hodgkin's disease. These cells represent the developmental cycle of the megakaryocyte. Mitosis just above center of field. Such a histopathological picture we regard as typical and as sufficient to justify a diagnosis of Hodgkin's disease. × 1000.

FIG. 20. Another area from same section as Fig. 19. Shows an area of necrotic tumor heavily infiltrated with neutrophiles. × 1000.



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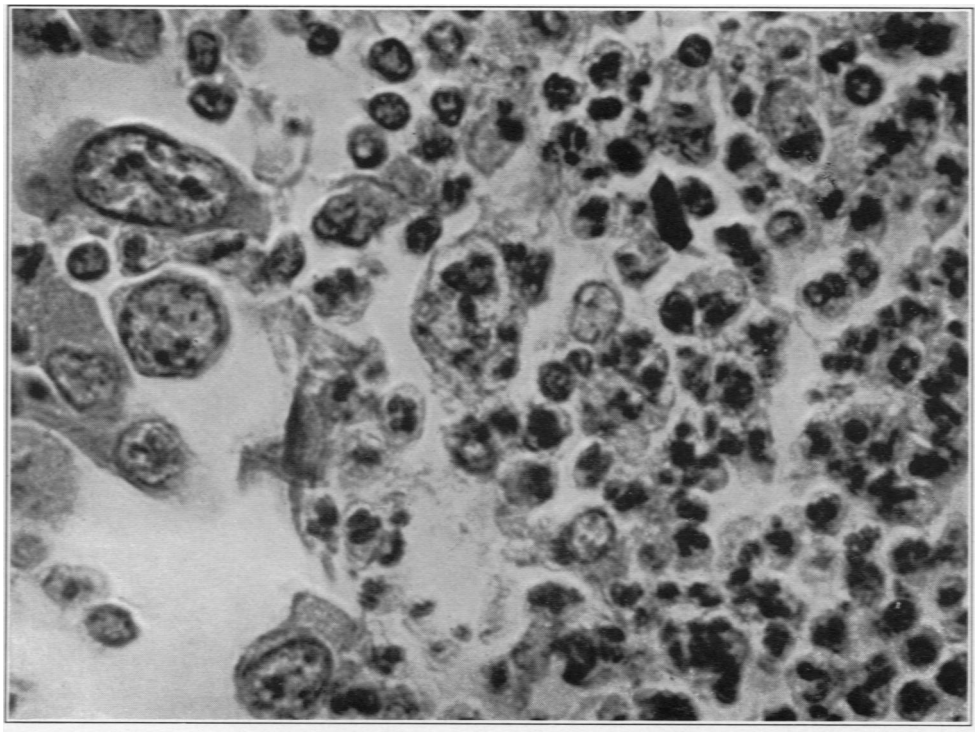

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