AN EVALUATION OF STERNAL ASPIRATION AS AN AID IN DIAGNOSIS OF THE MALIGNANT LYMPHOMATA

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The diagnosis of malignant lymphoma can be definitely established only by histologic examination of the tissue involved. In the majority of instances palpably enlarged superficial lymph nodes are present and properly performed biopsy provides the correct diagnosis in a direct and relatively simple manner. However, in a significant number of cases of Hodgkin's disease, lymphosarcoma and follicular lymphoma the primary site of involvement is thoracic, abdominal or some otherwise inaccessible location for simple biopsy.

Symmers has stated that in Hodgkin's disease primary enlargement of abdominal or abdominal and thoracic nodes combined is ten times more common than primary enlargement of the cervical nodes. Ewing supported this view, emphasizing that the superficial nodes which first attract attention may be only the outlying manifestations of an internal lesion. Jackson and Parker found the superficial nodes primarily involved in all of 26 cases of Hodgkin's paragranuloma, but in only 8 of 59 cases of Hodgkin's granuloma, and in none of 27 cases of Hodgkin's sarcoma. Sugarbaker and Craver regarded the primary site of involvement as extranodal in approximately one third of 196 cases of lymphosarcoma. In 14.2 per cent of cases in which lymph nodes were involved primarily, the site of origin was abdominal or mediastinal. These observations contrast clearly with the common impression that superficial lymph nodes, particularly those of the cervical area, constitute the usual site of primary involvement in these conditions.

Biopsy of superficial nodes, then, may be of no value in establishing a diagnosis in some cases and of value only after the disease process is well advanced in others.

This study was undertaken in an attempt to evaluate the clinical usefulness of aspiration of sternal bone marrow as a method for obtaining material of diagnostic significance in cases of malignant lymphoma.

Review of the Literature

Bone or bone marrow involvement in cases of malignant lymphoma

Hodgkin's disease. The dominant histologic change in Hodgkin's disease involves the reticular cells of the reticulo-endothelial system. The lymphatic elements do not take an active part in the hyperplasia in most cases and often are diminished in number. It might reasonably be expected that an organ rich in reticulo-endothelial tissue as is the bone marrow would be commonly involved in the disease.

Steiner, in his comprehensive review of the subject, suggested that bony lesions might develop in one of three ways: (1) by direct invasion from contiguous
lymphogranulomatous masses, (2) by hematogenous spread or (3) by primary origin in the marrow.

Krumbhaar reported a case of Hodgkin's disease of the bone marrow and spleen without apparent involvement of lymph nodes. Herscher and Livingston observed cases in which, at autopsy, the process appeared to be confined to the bones and liver.

The reported incidence of bone or bone marrow involvement in Hodgkin's disease is highly variable, particularly in studies based on clinical evidence alone. In summarizing the reported series in which the diagnosis of bone or bone marrow involvement was based on clinical grounds, Steiner determined an average incidence of 8.3 per cent (166 of 2,006 cases). Lesions of bone most frequently involving the spinal column and pelvis, were noted during life in 23 per cent of Jackson and Parker's 133 cases of Hodgkin's granuloma. Similar lesions were detected in 14.8 per cent of 257 cases of Hodgkin's disease reported by Vieta and co-workers.

The latter authors called attention to cases of extensive marrow involvement discovered at postmortem examination in which the same bones had appeared normal on previous roentgenologic examination. The degree of cortical involvement appears to determine to a considerable extent the roentgenographic appearance of bone, and extensive medullary lesions may not be detected by this method.

According to Ewing, bone marrow lesions, both typical and atypical, form a prominent feature in many cases of Hodgkin's disease; at times they may dominate the clinical course and it is rare that a thorough search at autopsy fails to disclose some deposits in the bone marrow. Steiner noted an average incidence of 28.3 per cent of bony lesions in 547 reported autopsies but observed that the incidence reported from any series apparently depended on the thoroughness of the skeletal examination. He studied microscopic sections taken at random from 3 to 9 easily accessible bones in 14 cases of Hodgkin's disease and found marrow lesions in 78.6 per cent of cases. The vertebrae, pelvis, ribs, femur, sternum, skull and humerus were most commonly involved. Sixty-three and seven-tenths per cent of sternal sections contained lymphogranulomatous lesions. Steiner further observed that there was no basis for the impression that skeletal lesions occur only as a late manifestation of Hodgkin's disease.

Lymphosarcoma. By original definition, lymphosarcoma lacks the systemic character of Hodgkin's disease and leukemia. Arising as an apparently local change in lymphadenoid tissue, it seems to extend by local invasion, by continuous growth through lymph channels and by the formation of true metastatic lesions in distant organs.

Lymph vessels have not been demonstrated in bone marrow but small accumulations of lymphatic tissue along the small arteries have been described by most investigators. Lymphosarcoma might, then, arise in the bone marrow but this structure would seem no more likely to become secondarily involved than would any other organ.

Sugarbaker and Craver noted clinical evidence of bony involvement in 9.7 per cent of 196 cases of lymphosarcoma. In 1 per cent, the process appeared to arise in bone marrow. Vieta and co-workers found roentgenologic evidence of bony
involvement in 7 per cent of 213 cases, while on postmortem examination lesions were noted in 19 per cent of 54 cases. The authors regarded the latter figure as probably too low since the examinations at necropsy were limited to easily accessible bones and the skeletal examination was sometimes omitted entirely. Lesions of bone in this series were most often a late manifestation of the disease. Such lesions appeared in only 22 per cent of cases during the first half of the course of the illness while in 65 per cent the bony involvement appeared to develop during the terminal one third of the illness. By contrast, in cases of Hodgkin's disease observed by the same authors, 37 per cent of the bony lesions were clinically evident before the first half of the course of the disease had elapsed. It was further observed that while the bony lesions in lymphosarcoma were, as in Hodgkin's disease, most common in the bones rich in red marrow there was a tendency for a more generalized distribution of lymphosarcomatous lesions to occur.

The less detailed observations of other authors11, 14–18 would indicate that bone marrow involvement in lymphosarcoma occurs infrequently and then as a manifestation of a late, generalized stage of the disease.

Follicular lymphoma. Sugarbaker and Craver4 have regarded follicular lymphoma as a "setting" for lymphosarcoma since later biopsies in several of their cases have shown the development of "typical reticulum cell lymphosarcoma." Whatever the exact relationship between the two processes may be, it appears to be an intimate one.

Gall and co-workers19 noted bony lesions (clinically evident) in 6 of a series of 63 cases of the follicular type of malignant lymphoma.

Reported clinical experience with sternal aspiration in cases of malignant lymphoma

Hodgkin's disease. Young and Osgood20 found that study of specimens of aspirated sternal marrow was of "no diagnostic value" in 2 cases of Hodgkin's disease. Vogel and co-workers21 observed a "slight left shift" and, in a few cases, an increase in eosinophils and reticulum cells. It was noted that 3 of the 5 patients studied had received intensive irradiation therapy during the year preceding the examination of the sternal marrow. Émile-Weil and Perlès22 obtained negative or inconclusive results in most cases. In 10 of 25 instances, medullary hyperplasia was noted. A slight increase in polymorphonuclear neutrophils, eosinophils, plasma cells and monocytes was commonly observed. Although no Reed-Sternberg cells were noted the authors suggested that the differentiation of such cells from megakaryocytes would be difficult. Paraf and co-workers23 reported 1 case in which a sternal tumor was present. Sternal aspirations at three sites yielded material suggesting only erythromyeloid aplasia with lymphocytes and plasma cells predominant. After study of the findings in 14 cases Falconer and Leonard24 observed "the sternal marrow in this group in some instances showed a leukemoid or myeloid reaction difficult to distinguish from the early myeloid reaction of myelogenous leukemia." In only 1 case was the specimen of sternal marrow the basis for the diagnosis of Hodgkin's disease; a trephine specimen which revealed "fibrosis" was obtained in this case.

Scott25 examined specimens in 8 cases and concluded that the findings, while
dependent on the stage of the disease, were variable and nonspecific. In none were Reed-Sternberg cells found. In 3 there were varying degrees of myeloid left shift. In 2 some increase in number of megakaryocytes was noted. One patient presented aplastic changes which were attributed to previous irradiation therapy. Baras-rucci26 reported 6 cases in which marked eosinophilia of the marrow occurred. Mendell and co-workers27 noted no characteristic changes in specimens of marrow from 3 patients. Propp and Schwind26 stated that "myelophthisic anemia such as occurs in Hodgkin's disease and reticulosis are among the diseases giving marrow pictures which are not diagnostic." Piney and Hamilton-Paterson29 stated that "we probably never obtain assistance in diagnosis by examining the bone marrow in Hodgkin's disease." and described hyperplastic and hypoplastic changes in varying stages of the disease. Sundberg30 and Wintrobe31 agreed that the usually encountered marrow picture is nonspecific, consisting of some shift to the left in the myeloid line together with a slight monocytosis or eosinophilia. Limarzi32 reported myeloid hyperplasia, an increase in plasma cells, histiocytes and megakaryocytes in some cases of Hodgkin's disease.

While the majority of investigators have found aspiration of sternal marrow of little value as a diagnostic procedure in Hodgkin's disease, there are a few exceptions. Váradi33 reported a single case in which sternal aspiration yielded a specimen containing many lymphocytes and large basophilic cells with large nuclei and large, blue nucleoli which he classified as Reed-Sternberg cells. Rohr and Hegglin34 identified Reed-Sternberg cells in the specimen of marrow in a case of Hodgkin's disease. Klima35 described a "lymphogranulomatellen," which he felt to be a derivative of the lymphoblast, as the characteristic cell of Hodgkin's disease. Scott35 regarded the cell described by Klima as a "partly differentiated reticulum cell such as is frequently seen in imprint and puncture preparations from lymph nodes of many conditions other than Hodgkin's disease." From 1 patient Sundberg30 described section preparations showing the granulomatous lesions typical of Hodgkin's disease, but "only after an extremely diligent search" was a single Reed-Sternberg cell found in smear preparations from the same patient.

**Lymphosarcoma.** Dameshek and co-workers36 in illustrating the comparative value and limitations of trephine and simple aspiration methods of sternal marrow biopsy reported 2 cases of lymphosarcoma. On attempted aspiration "no cells" were obtained in 1 and "very few cells" in the other case. Study of sections obtained by the trephine method established the diagnosis in each case, disclosing "lymphosarcoma with connective tissue replacement of the marrow" in the first, and "a small area of lymphoblastic proliferation (lymphosarcoma)" in the second. Vogel and co-workers37 reported "the marrow findings essentially normal" in 4 cases of lymphosarcoma and in 2 of follicular lymphoma. Falconer and Leonard34 found that study of aspirated marrow material was of "no aid to diagnosis" in 4 cases of lymphosarcoma. Wintrobe30 noted an increase of lymphocytes in some cases of lymphocytic lymphoma and in 1 of follicular lymphoma, but more commonly he found no abnormality in the marrow in such cases. Gormsen,37 in 2 of 18 cases of lymphosarcoma, observed moderate infiltration of the sternal marrow with more or less immature lymphatic elements.
STERNAL ASPIRATION IN MALIGNANT LYMPHOMATA

MATERIAL AND METHODS

Material. The material for this study was obtained by simple needle aspiration of sternal bone marrow in 15 unselected cases of Hodgkin’s disease, 10 of lymphosarcoma and 2 of follicular lymphoma. The diagnosis in each case was based on results of lymph node biopsy, autopsy or both.

Because of the uniformly poor results reported following examination of simple smears after needle aspiration, no cases were included in this series in which examination was carried out prior to the introduction, for routine use in this laboratory, of the methods of preparation advocated by Schleicher.

Technic. With the Illinois sternal aspiration needle a total of approximately 2 cc. of sternal marrow substance was aspirated. The specimen was transferred immediately to a paraffin-lined container and mixed gently with a minute pinch of heparin powder as an anticoagulant.

Portions of the material obtained were used for preparation of the usual smears, Wright’s stain (Grübler) being used and for “volumetric” determinations. The latter procedure has been found to provide a fairly accurate quantitative index of the functional state of the marrow.

The grossly visible particles of marrow substance, or “units,” in the aspirated specimens were carefully collected. These units ranged from 0.5 to 1.0 mm. in diameter in the normal individual to as much as 0.3 to 4.0 mm. in the hyperplastic marrow of pernicious anemia. Several of these units were speared on the tip of a wooden applicator and the material smeared out gently on the surface of a glass slide. The resulting imprint preparations provided a picture of the general structural relationships of the marrow.

Finally, after fixation, the remaining units were stained with hematoxylin and eosin and “section” preparations obtained. Sections so prepared provide architecturally and histologically accurate samples of the marrow. With this method, it has been felt that the needle aspiration method more closely approaches a true biopsy procedure, and the advantages of the trephine method have been, to a considerable extent, overcome. It was hoped that aspirated material so prepared would yield information of diagnostic significance in circumstances in which the simpler aspiration and smear technics had reportedly failed.

Plan of study. The preparations described above were carefully examined. Differential counts of 1,000 nucleated cells were carried out in each case. The clinical features in the cases under consideration were analyzed and some correlation with the appearance of the marrow specimen was attempted.

RESULTS OF STUDY

Hodgkin’s disease

Criteria for diagnosis. Hodgkin’s disease of the bone marrow exhibits the same histologic picture seen in other involved tissues and organs. Hyperplasia of reticular cells is often the dominant change. However, the process is characterized by

* Manufactured by the V. Mueller Co., Chicago, Ill.
pleomorphism and the diagnosis rests finally on the demonstration of the presence of Reed-Sternberg cells, whether the pathologic change be paragranulomatous, granulomatous or sarcomatous in type.3

Piney and Hamilton-Paterson29 have stated that "there is no certain way of distinguishing Reed-Sternberg cells from megakaryocytes." While it is true that the differentiation may be difficult, it is felt that it can be satisfactorily accomplished in most instances if undistorted, properly stained cells are considered.

The mature cells are similar in size. The nuclei of Reed-Sternberg cells are round, oval, lobulated, multilobed or multinucleated. The nuclear chromatin is relatively scanty in amount and irregularly distributed (fig. 1). Megakaryocytic nuclei, although often multilobed, are always single with generous, more uniformly distributed chromatin and a fine chromatin-parachromatin pattern. The outstanding characteristic of the Reed-Sternberg cell is the very prominent nucleolus (fig. 1b) which is usually lacking in the megakaryocyte or megakaryoblast. The cytoplasm of the normal megakaryocyte contains characteristic azurophilic granulation when stained with the polychrome dyes. In addition, pseudopodia with apparent platelet formation are often observed. The generous cytoplasm of the Reed-Sternberg cell has a faintly basophilic, granular appearance with Wright's stain and the cell membrane is often indistinct.

Results. Detailed search of all material obtained by sternal aspiration in the
proved cases of Hodgkin's disease in this series revealed no Reed-Sternberg cells. Satisfactory section preparations were obtained in 9 instances but in none were lesions suggestive of Hodgkin's disease demonstrable.

In 6 instances, the specimen of marrow appeared normally active, and in 5 there was distinct hyperplasia. Other variations from normal in this group were minor in degree and of nonspecific character, consisting of myeloid preponderance with slight shift to the left in 5, mild eosinophilia in 3, toxic changes in cells of the myeloid series in 4 and diminished erythrogenic activity in 3. One or more of these changes was present in each case.

In the remaining 4 cases, attempted aspiration resulted in a relatively "dry tap," although a few drops of marrow were obtained from which smears were made. Such a result with this procedure in the hands of an experienced individual should, per se, raise suspicion of disease of the marrow. It has occurred most often in cases of myelofibrosis, acute leukemia and metastatic carcinoma involving the bone marrow. In Hodgkin's disease the attempted aspiration is probably defeated by the fibrous character or hypercellular consistency of the involved tissue. In this connection, Loseke and Craver experienced difficulty in obtaining satisfactory or sufficiently large specimens in 11 of 25 cases of Hodgkin's disease in which needle aspiration of lymph nodes and other involved tissues was attempted. Smear preparations in 1 of the 4 "dry tap cases" revealed few normal marrow elements with small lymphocytes composing 91 per cent of the nucleated cells; in the remaining 3 cases there was an increase in number of morphologically normal lymphocytes with moderate reduction in number of erythrogenic and myeloid cells.

It should be emphasized that despite the negative findings on sternal aspiration, demonstrable bone or bone marrow involvement was present in 4 cases of this series. The dorsolumbar vertebrae were the site of the clinically evident lesions in 3 while in the remaining case the clavicles and several ribs were involved.

No correlation could be established between the marrow findings and the duration of the disease, the apparent degree of dissemination of the process, the amount of previous irradiation therapy or the peripheral blood picture. A mild to moderately severe anemia, hypochromic in type, was noted in 11 of the 15 cases in this group. The anemia was accompanied by evidence of active regeneration of erythrocytes, including the presence of macrocytes and polychromatophilia, in 9 instances. Monocytosis was noted in 6, myeloid immaturity in 4 and eosinophilia in 3.

Comment. No consistent abnormalities or diagnostically specific changes were encountered in the study of sternal marrow material in this series of cases of Hodgkin's disease.

The occurrence of "dry taps" in 4 instances was regarded as suggestive of marrow involvement but careful examination of the smears made from the meager specimens obtained disclosed nothing of diagnostic significance.

The lesions of the bone marrow in Hodgkin's disease may be focal and of microscopic proportions or extensive and grossly demonstrable. When small, focal lesions exist, chance alone might account for disappointing results on attempted needle aspiration. Aspiration of marrow material from several sternal sites, from vertebral bodies, and perhaps, from the iliac crest might enhance the diagnostic po-
potentialities of the procedure. In addition, the sternum should be routinely palpated for areas of tenderness and such localities should be selected as the site for aspiration.

The fibrosis which so commonly develops in the lesions of Hodgkin's disease could conceivably render simple aspiration of a satisfactory specimen impossible. Utilization of the trephine method, in "dry tap" cases particularly, might overcome this difficulty.

The high incidence of positive findings on sections taken at random post mortem by Steiner would indicate that more frequent positive results should follow the adoption of the proper technic. This should be particularly true in patients presenting clinical or hematologic evidence of bone marrow involvement.

Lymphosarcoma

Criteria for diagnosis. No one cell has been shown to be diagnostic of lymphosarcoma. Ghon and Roman emphasized the usual presence of a mixture of cells and commented that lymphosarcoma appears to be a neoplasm in which all elements of the normal lymph node may be represented. These cells ranged from typical small lymphocytes through larger, atypical cells with indented, hyperchromatic nuclei and relatively little cytoplasm, to lymphoblastic cells with reticular nuclear structure, sometimes containing nucleoli, and a basophilic, often vacuolated, cytoplasm. Lymphocytic, lymphoblastic and reticulum cell varieties of lymphosarcoma have been commonly described. Gall and Mallory subdivided lymphosarcoma into stem cell, clasmatoeytic, lymphoblastic and lymphocytic types, according to the predominant cell type. Hellwig has advanced a similar classification.

Sternberg, however, described a cell which he regarded as characteristic of lymphosarcoma, occurring in cases of so-called leukosarcoma. Sternberg considered the cell a form of lymphocyte but, at the same time, an atypical tumor cell. The majority of hematologists have not accepted leukosarcoma as an entity and prefer to consider it a locally aggressive type of leukemia, most often large cell and acute in type.

Isaacs noted the development of leukocytosis in 15 of 43 cases of lymphosarcoma. He described a "characteristic" cell appearing in the peripheral blood in those cases of "lymphosarcoma cell leukemia" which he felt was usually mistaken for an immature lymphocyte or lymphoblast. Certain distinguishing features of the nucleoli were stressed. When stained with Wright's stain after the material has been smeared on cover slips treated with cresyl blue, "the nucleolus stands out as a sky blue, round area surrounded by a deep blue-black rim of cytoplasm" which is piled up around it. Such nucleoli were usually single. In contrast, nucleoli of immature lymphocytes or lymphoblasts appeared as "a light blue hole in the chromatin structure," without the heavily staining rim. In addition, the chromatin around the edge of the nucleus of the lymphosarcoma cell was "thickened into a fairly definite nuclear wall." In 6 of the 15 cases in this group necropsy disclosed "transformation, in varying degrees, of all lymphoid tissue in the body into the lymphosarcoma type." The autopsy findings cited in these cases would seem more consistent with the diagnosis of leukemia than lymphosarcoma.
Wiseman said it is possible, by use of vital staining methods, to differentiate normal, leukemic and lymphosarcomatous lymphocytes.

Gall and Mallory considered the development of a leukemic blood picture an incidental manifestation of the underlying neoplastic process in lymphosarcoma. Blood pictures resembling leukemia occurred at some time in the course of the disease in 18 per cent of the lymphocytomas and in 28 per cent of the lymphoblastomas reviewed by Hellwig. Evans and Leucutia advanced the concept that lymphosarcoma becomes leukemia when the bone marrow is involved.

Webster regarded lymphosarcoma, lymphatic leukemia and leukosarcoma as manifestations of the same disease. There appears to be little doubt that the processes are closely related, and absolute differentiation is commonly difficult and sometimes impossible.

In addition to the doubtful existence, according to the majority of investigators, of a cell characteristic of the disease, the positive microscopic diagnosis of lymphosarcoma is further complicated in that the general histologic picture may be closely simulated in other conditions, notably Hodgkin's sarcoma and lymphatic leukemia. Potter suggested that the diagnosis of small cell lymphosarcoma should be eliminated from consideration in lymph node enlargements and labeled aleukemia.

Results of study. Material permitting satisfactory section, imprint and smear preparations was obtained in all cases in this group; however, the technical difficulty encountered was sufficient to warrant the designation 'dry tap' in 2 instances.

In 3 cases the specimen of marrow presented no remarkable deviation from the normal. Lymphocytosis, ranging from 30.6 to 70.9 per cent with an average of 46.2 per cent, was present in the remaining 7 cases. The lymphocytosis was accompanied by moderate to marked diminution in number of erythrogenic cells. In contrast to the frequent finding of myeloid hyperplasia with left shift in cases of Hodgkin's disease, such changes were not observed in this group.

The fixed sections presented the most spectacular findings. In 3 instances the marrow was infiltrated or invaded by obviously abnormal tissue composed of mononuclear cells (fig. 2). The picture presented was one of focal involvement, with apparently uninvolved marrow tissue interspersed. This contrasts with the usual appearance of the marrow in lymphatic leukemia (fig. 3) in which, while nodules of lymphocytes may be present, the involvement is usually more diffuse in character. This difference may not be striking on superficial examination (figs. 3a and 4a) but on closer study cells of the myeloid and megakaryocytic series can be identified even in a densely infiltrated marrow in chronic lymphatic leukemia (fig. 3b). On the other hand, no normal marrow elements can be identified among the lymphocytic cells composing the infiltrate in cases of lymphosarcoma (fig. 4). Whether this distinction will be sufficiently consistent to be regarded as definitely diagnostic can be determined only by study of more cases.

Fixed sections in the remaining cases appeared normal in 3 instances and presented varying degrees of hypoplasia, without aggregations of mononuclear cells, in 4.
In 3 cases there was no significant deviation from the normal either in the morphologic character of the lymphocytes or in other features observed on the smear preparations. Atypical and abnormal lymphocytic types were present in all 7 cases in which there was some degree of lymphocytosis in the marrow specimen. No single lymphocytic type predominated in these cases but rather a variety of forms was encountered on the smear preparations. The prevailing types could be loosely separated into the following categories:

**Type 1:** This was a large (10 to 18 micra) round to oval cell containing an irregularly shaped, frequently indented nucleus with relatively scanty, basophilic cytoplasm (fig. 5a). The dense chromatin material was uniformly distributed with little parachromatin evident. Distinct nucleoli were fairly numerous.

**Type 2:** Similar in size (14 to 18 micra) to the cells described as type 1, this cell (fig. 5b) demonstrated less bizarre nuclear configuration and more generous, basophilic cytoplasm. The nuclear structure was reticular with frequent "grooving" and occasional indistinct nucleoli. A clear perinuclear zone was occasionally observed.

**Type 3:** These cells (fig. 5b) were 8 to 12 micra in diameter and presented dense, hyperchromatic, frequently "grooved," occasionally Rieder-type nuclei with a very...
thin rim of deeply basophilic cytoplasm. This was the abnormal cell type most commonly encountered.

Type 4: These cells (fig. 5c), measuring 14 to 20 micra in diameter, appeared much like normal large lymphocytes but contained "smoothed out," irregular shaped, often eccentrically placed nuclei with rare indistinct nucleoli. The cytoplasm was sky blue in color and presented occasional azure granules.

These atypical or abnormal cells were seen in company with varying proportions of lymphocytes having a morphologically normal appearance. While a single type of abnormal cell was usually predominant in each case a mixture of types was most commonly encountered (fig. 5b). No correlation could be made in this series between the type of cell predominating in the sternal smear and the type according to the morphologic classification advanced after biopsy and autopsy.

The cell types observed might be confused with, or may indeed be identical with, atypical or bizarre forms sometimes encountered in subacute or acute lymphatic leukemia but are clearly distinguishable from the ordinary lymphocyte or lymphoblast.

In 5 of the 7 cases in which atypical lymphocytes were demonstrated in the marrow specimen, similar cells were observed in smears of the peripheral blood. In 4 of these, including the 3 cases in which there were "positive" fixed sections, peripheral lymphocytosis ranging from 36 to 64 per cent was noted at some time.
FIG. 4.—LYMPHOSARCOMATOUS INFILTRATION OF MARROW. Section preparations stained with hematoxylin and eosin. a. X 140. b. X 760.

FIG. 5.—SMERAR PREPARATIONS OF MARROW FROM A PATIENT WITH LYMPHOSARCOMA STAINED WITH WRIGHT'S STAIN. a. All type 1 predominates (X 675). The section preparation is shown in figure 2. b. Cell types 2 and 3 are illustrated. Section preparation is shown in figure 4 (X 720). c. Cell type 4 is illustrated (X 750).
during the period of observation. The total leukocyte count per cubic millimeter of blood ranged from 3,700 to 17,500 for the entire group.

No other abnormalities were consistently noted on study of the peripheral blood in these cases although minor degrees of myeloid immaturity and erythrocytic regeneration were occasionally observed. Despite the diminution in number of erythrocytic cells commonly noted (7 cases) on examination of sternal specimens, mild normocytic anemia occurred in only 2 cases.

No clinical evidence of bony involvement was noted in this group. In all cases superficial lymph nodes were palpably enlarged, the lymphadenopathy involving the anterior cervical, axillary and inguinal groups with approximately the same frequency. The spleen was palpably enlarged in 60 per cent. In no case was remarkable hepatomegaly demonstrated. The duration of symptoms prior to sternal aspiration ranged from two months to five years with the average duration of illness being shorter (eleven months) in the patients presenting most marked changes in the bone marrow. A history of previous irradiation therapy was elicited in 4 cases but could not be correlated with the findings noted on examination of the marrow in these cases.

Comment. The high incidence of abnormal findings in this group of cases was surprising. It is felt that the demonstration of lymphocytic 'tumor' infiltrates in the bone marrow should have the same diagnostic significance as the same finding in a lymph node or other tissue would have. The greatest difficulty will probably be experienced in histologically differentiating this picture from that of lymphatic leukemia.

While the specific diagnostic significance of the abnormal cell types encountered in 7 of the 10 cases in this group must be further evaluated, their presence in the bone marrow or peripheral blood would appear to justify the suspicion that lymphosarcoma exists.

Follicular lymphoma

This condition, which appears to be closely related to lymphosarcoma, is characterized histopathologically by the development in lymphoid tissue of multiple, follicle-like nodules of variable size. The predominant cell type in such a process has been described as an ordinary lymphocyte or lymphoblast.

In 2 cases reported by Baggenstoss and Heck, later biopsies revealed the picture of lymphosarcoma.

Satisfactory specimens were obtained in the 2 cases composing this group. In 1 instance there was a slight increase in number (20 per cent of nucleated cells) of morphologically normal lymphocytes. In the other, a hyperplastic specimen with preponderance of the myeloid line was obtained. Neither presented features of diagnostic significance.

In each, the spleen and superficial lymph nodes were moderately enlarged. The marrow lymphocytosis noted in the first case was not reflected in the peripheral blood which, but for a mild normocytic anemia, appeared normal. In the second case, leukopenia (1,400 leukocytes per cubic millimeter of whole blood) with a relative lymphocytosis and monocytosis was present. The patient had recently
completed a course of irradiation therapy before examination at the clinic. Symptoms had developed twelve to eighteen months prior to sternal aspiration. No clinical evidence of bony involvement was demonstrated in either case.

Comment. While sternal aspiration in these cases provided no information of diagnostic significance it is felt that, in view of the close relationship between follicular lymphoma and lymphosarcoma, study of a larger series of cases may well reveal more significant changes.

SUMMARY AND CONCLUSIONS

Neither diagnostically significant features nor consistent abnormalities of other character were demonstrated in the specimens of sternal marrow obtained in 15 cases of Hodgkin's disease. With improvements in technic, particularly in patients presenting clinical evidence of bone or bone marrow involvement, the procedure might become more valuable.

As an aid in diagnosis in cases of obscure malignant lymphoma, sternal aspiration is likely to prove of greatest value in cases of lymphosarcoma. In 7 of 10 proved cases, abnormal lymphocytic cell types were encountered and in 3 instances bone marrow infiltrations were demonstrated in fixed section preparations. The latter were felt to be diagnostic of lymphosarcoma.

In 2 cases of follicular lymphoma the specimens of sternal marrow presented no striking abnormalities. However, because of the apparently close relationship which this disease bears to lymphosarcoma it is felt that study of a larger number of cases may prove the procedure of some diagnostic value.

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