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JUAN A. DEL REGATO, M. D. *Editor*

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MALIGNANT TUMORS OF THE LYMPHOID STRUCTURES

For years we have endeavored to devote one of these conferences to the protean group of tumors which made the subject of this Eighteenth Annual CANCER SEMINAR. Thanks to the help of our contributors, we were able, finally, to gather a group of such cases with a radiologic and/or histopathologic interest.

As the reader of these proceedings will easily conclude, this area of histopathology of tumors is not only fraught with pitfalls for the unsophisticated pathologist, it is also in great need of a semantic covenant that might facilitate didactics while accommodating different histogenetic theories. Few other tumors are as discouraging to the neophyte; in his confusion and frustration the young initiate is likely to be pushed into irresponsibility and bluff. In an area where there is so much confusion among pathologists, it is only to be expected that radiologists, as well as hematologists and other specialists, find it difficult to make their own contribution. In this CANCER SEMINAR only one case failed to be diagnosed, by at least a few pathologists, as a case of Hodgkin's disease (see asterisk in the histopathologic tabulations); such indiscriminate diagnosis of a rather well defined clinical entity leads to misunderstanding, unawareness of therapeutic possibilities and mistreatment of a large number of patients.

For this occasion we were fortunate to secure the keen diagnostic gifts of Dr. H. Mellins who acquitted himself admirably of a very difficult task. Dr. H. Rappaport, the unquestionable high authority in the histopathology of these tumors, demonstrated the secret of his excellence: a demanding attitude in reference to technique and interpretation. In addition to his didactic discussions, we owe Dr. Rappaport the careful redaction of the captions of photomicrographs in this issue. The discussions of each case were enlivened by the participation of our knowledgeable third guest, Dr. Jesse Steinfeld, a young internist with few peers in the field of chemotherapy of tumors.

This CANCER SEMINAR was attended by 540 pathologists, radiologists, internists and other specialists. We wish to thank the contributors, our guest speakers and the participants for the continued success of these educational exercises.

J. A. del REGATO, M. D.

Colorado Springs, Colorado
August, 1967

1. *Granulocytic Sarcoma of the Orbit (Chloroma)*

Contributed by W. T. SNODDY, M.D. and E. H. KALMON, M.D.

Oklahoma City, Oklahoma

THE PATIENT was a 9-year old boy in July, 1963, when he presented with a recent swelling of the left lower eyelid. On examination there was a non-ulcerated subcutaneous tumefaction of the eyelid, measuring 1 cm and extending to the infraorbital region; eyes and vision were normal; there was no palpable cervical adenopathy. The hemoglobin was 13.9 gm %; there were 3% eosinophiles in the differential white blood count; the bone marrow was normal.

Dr. Mellins: There is a homogeneous opacity over the lower half of the left orbit which extends beyond the orbit and appears to represent soft tissue swelling of the lower eyelid. The transverse diameter of the lower portion of the left orbit is slightly greater than the right. A rounded soft tissue mass projects into the left maxillary antrum from the superior surface. There is, decidedly, mucous membrane thickening in the right maxillary sinus. The ethmoid and sphenoid sinuses do not appear abnormal on the postero-anterior projection. The maxillary sinuses are represented only by ethmoidal bullae. No clear evidence of bone destruction in the facial bones is seen.

A soft tissue density arising from the superior wall of the maxillary sinus produces the so-called superior polyp sign. Inflammatory polyps, mucous cysts and things of this nature do not arise in this area. If the process involves both antra in the present case, it would favor a diagnosis of the systemic rather than a local lesion. Histiocytosis X, as well as malignant reticulo-histiocytosis, can affect the orbits. The former usually produces lytic defects in the adjacent bone but it is possible that these are present without roentgen evidence. Among the malignant lesions, one must consider the primary processes of rhabdomyosarcoma and neuroblastoma and the secondary processes of Wilm's tumor and lymphoma. Rhabdomyosarcoma is more common in girls than in boys and may arise from the soft tissues anywhere on the face and head. Neuroblastoma occurs with equal frequency in boys and girls and arises from neural elements in the orbit. It has been considered a lymphoepithelioma or a transitional carcinoma. The patients are usually over seven. Wilm's tumor may metastasize to the orbit. One would expect clinical signs of an abdominal mass or specific presenting symptoms. Lymphosarcoma may first present in the maxillary sinus with involvement of the orbit and overlying skin. In the absence of palpable adenopathy or changes in the peripheral blood and the marrow, I would favor a diagnosis of histocytosis.

Dr. Mellins' impression: 1.) HISTIOCYTOSIS. 2.) LYMPHOSARCOMA.

Roentgenologic Impressions Submitted by Mail

Lymphosarcoma	24
Orbital lymphoma	9
Histiocytosis	12
Eosinophilic granuloma	17
Chloroma	8
Others	32

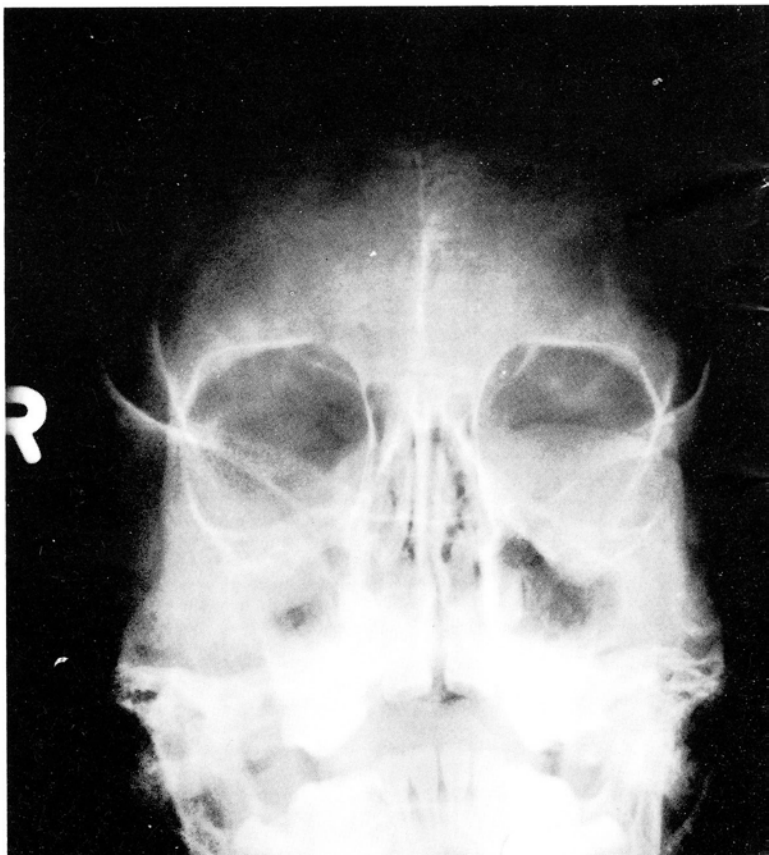
Dr. Mellins: The presence of the lid lesion, the involvement of the sinuses and orbit, encouraged some to consider this as a lymphosarcoma. I cannot exclude the possibility of a benign lymphoma in the orbit. We would have been more strongly for histiocytosis had we seen some localized bone lesions, but I see no reason why it could not exist without a bone lesion. Eosinophilic granuloma, I will consider in the same family. Chloroma is an important diagnosis, but I was bothered by the fact that there was no evidence of myelogenous leukemia in the marrow; we worried about this and decided not to call it chloroma because we had no evidence of leukemia.

Dr. Regato: Dr. N. W. Courtney, of Ann Arbor, suggested Hand-Schüller-Christian's disease; Dr. J. T. McClintock, of Denver, offered an impression of malignant lymphoma; Dr. J. C. Lemon, of Denver, preferred chloroma; Dr. E. Salzman, of Denver, and Dr. E. Nava, of Ann Arbor, offered rhabdomyosarcoma.

Operative findings: On July 15th, 1963, the tumefaction had doubled its size; it was removed through a conjunctival incision and was found to be well encapsulated.

Dr. Rappaport: The tumor is composed of cells that show considerable variations in size and shape. One is impressed with the similarity that this lesion has with lymphosarcoma, or what I prefer to call "malignant lymphoma, poorly differentiated lymphocytic type." On careful scrutiny one sees that the neoplastic cells have certain features that make them appear different from those seen in lymphosarcoma. First, there is a fairly even distribution of the nuclear chromatin; second, many of the cells have a larger amount of cytoplasm than the neoplastic cells of lymphosarcoma. The amount of cytoplasm is probably even greater than that demonstrated by these sections, since many of the empty spaces are artifacts of fixation and rep-

Fig. 1—Homogeneous opacity of the lower half of the left orbit representing soft tissue swelling of the lower eyelid.



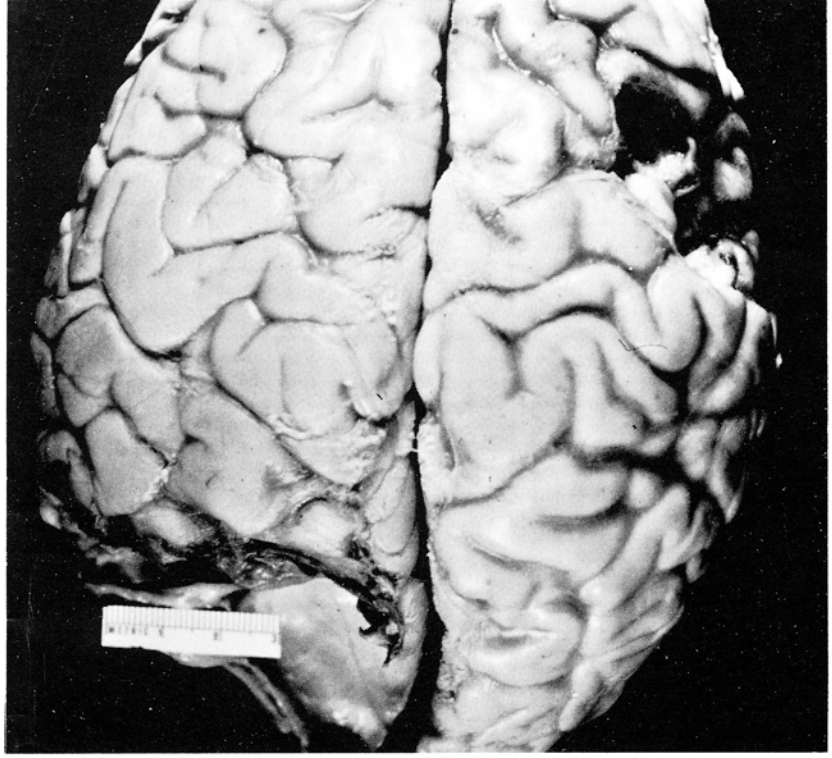


Fig. 2—Autopsy appearance of the surface of the brain.

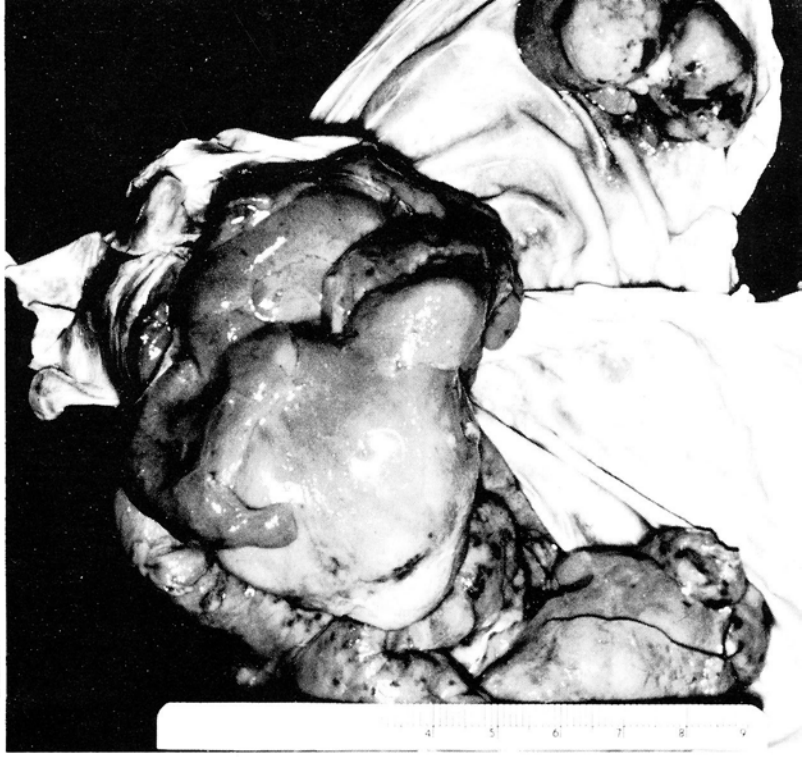


Fig. 3—These greenish masses were found adhering to the inner surface of the dura mater.

resent shrinkage of cytoplasm; one may find some that have distinctly eosinophilic granules (Fig. 4.). In some fields both mature eosinophilic granulocytes and eosinophilic myelocytes may be found; a Giemsa stain shows the eosinophilic granules even better. In cases of granulocytic malignancy the recognition of these eosinophilic myelocytes is of great diagnostic aid. The reason for this is that the basophilic granules are dissolved in aqueous fixatives and neutrophilic granules are not readily demonstrable in tissue section. However, from the presence of eosinophilic myelocytes, one can infer that neighboring cells with similar nuclear features are also myelocytes or their precursors, even though their granules are not evident in fixed sections. Based upon the identification of immature granulocytes, this orbital tumor was diagnosed as chloroma. There are many synonyms for chloroma. Personally, I prefer "granulocytic sarcoma" to chloroma because: 1) not all the tumors that have this cellular composition are green and 2) this is a sarcomatous tumor composed of granulocytes. Anyone who made the diagnosis of either chloroma, myeloid sarcoma, or even granulocytic leukemia made the correct diagnosis in this case. Chloromyeloma, myeloblastoma, myelocytoma, and myelosarcoma are other synonyms that have been used for designating this tumor.

A brief comment on the lack of demonstrable leukemia in the bone marrow and peripheral smears is in order: this does occur. The appearance of granulocytic tumors may precede the hematologic evidence of granulocytic leukemia, but as a rule a leukemic blood picture becomes apparent within a year. The difficulty of diagnosing granulocytic leukemia from tissue sections is even more apparent when one is dealing with lymph nodes, and it is there where the diagnosis is often missed. Clinically, chronic granulocytic leukemias may, at times, present with large lymph nodes and the erroneous diagnosis of lymphosarcoma or reticulum-cell sarcoma may be made unless the cytologic features of the lesion are carefully evaluated. Therefore, published reports of co-existing granulocytic leukemia and reticulum-cell sarcoma should not be accepted uncritically. In well preserved tissues sections, fixed in non-aqueous fixative, one can demonstrate the granules of the basophilic myelocytes. Large numbers of basophilic cells may be apparent in properly fixed Giemsa stained sections. An additional feature that is of diagnostic value is the presence of occasional normal or atrophic lymphatic follicles surrounded by a sea of immature granulocytes.

Dr. Rappaport's diagnosis: GRANULOCYTIC SARCOMA (chloroma).

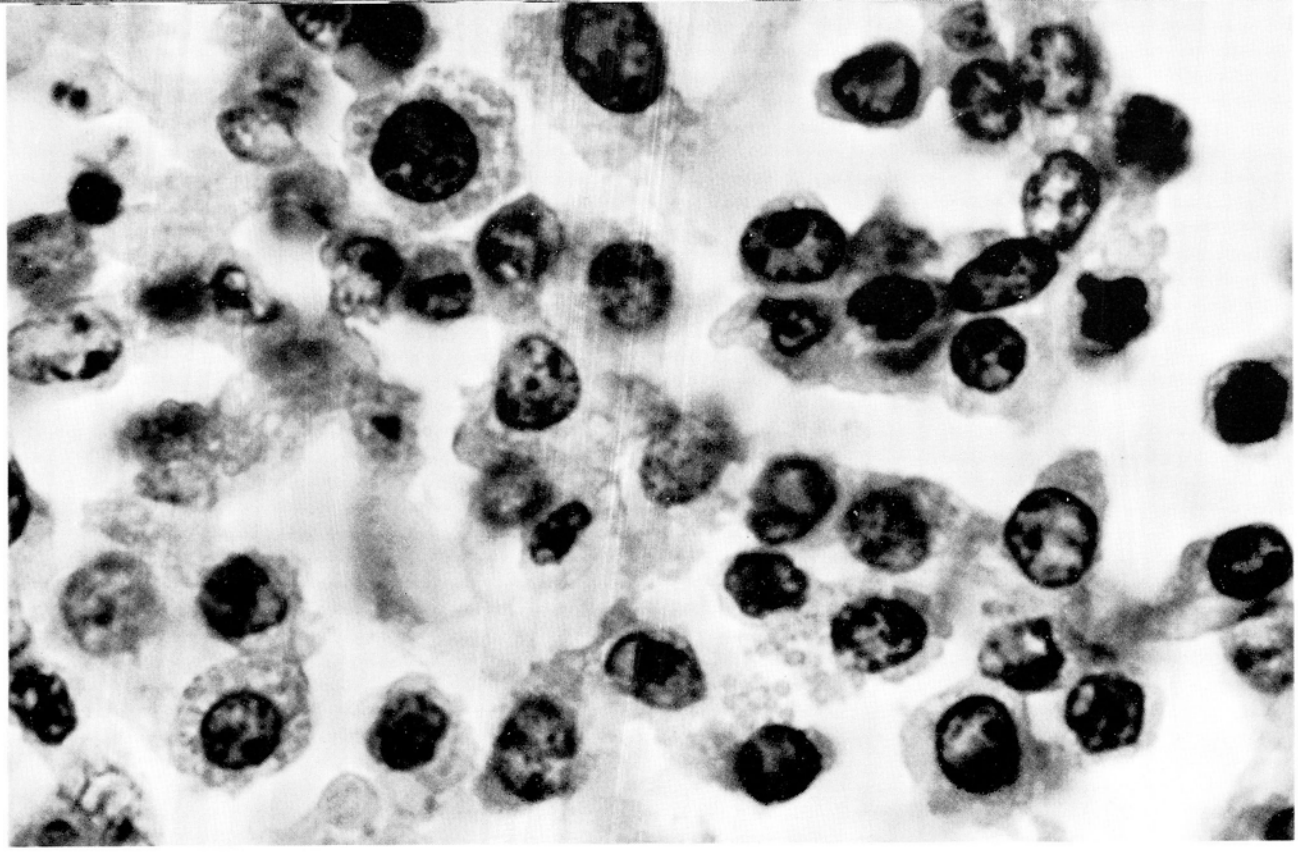
Histopathologic Diagnoses Submitted by Mail

Malignant lymphoma		40
histiocytic	11	
reticular	6	
lymphoblastic	2	
lymphocytic	5	
Myeloid leukemia (sarcoma)		35
Plasma-cell myeloma		33
Eosinophilic granuloma		14
Histiocytosis		13
*Hodgkin's disease		9
Ewing's sarcoma		6
Benign lymphoma		10
Rhabdomyosarcoma		15
Ten others		16

Dr. Rappaport: It can be seen that of the 190 diagnoses submitted by mail, only 35 or 18% were correct. The majority of incorrect diagnoses are those of malignant lymphomas of various types and of plasma cell myeloma. Only these two will be discussed. The diagnosis of malignant lymphoma, histiocytic type, is incorrect since the predominating cells are smaller than histiocytes and lack the coarse nuclear chromatin pattern of neoplastic histiocytes ("reticulum cells"). The undifferentiated lymphomas are composed of more uniform appearing cells that have scant cytoplasm and round to oval nuclei with delicate chromatin patterns. The differentiation from lymphosarcoma has already been discussed. The tumor cells of granulocytic sarcoma show little resemblance to plasma cells. Binucleated cells with nuclei of identical size and shape that are characteristic of plasmacytoma are lacking in this tumor.

Dr. Regato: Dr. R. Dorfman, of St. Louis, and Dr. Leo Lowbeer, of Tulsa, also made a diagnosis of chloroma; Dr. M. R. Abell, of Ann Arbor, offered erythrophagocytic myeloblastoma and Dr. H. van Auken, of San Antonio, preferred embryonal rhabdomyosarcoma.

Subsequent history: A diagnosis of reticulum-cell sarcoma of the eyelid was rendered and the patient received



2,000 R in 32 days during August, 1963. The slide was submitted to the A.F.I.P. and Dr. L. E. Zimmerman declared himself in favor of granulocytic leukemia but admitted that the bone marrow did not show corroborating evidence (A.F.I.P. Accession No. 1103418). The slide was submitted by the A.F.I.P. to Dr. Henry Rappaport, their consultant, who reported: "Eosinophilic myelocytes are identifiable among the less well differentiated tumor cells. I, therefore, regard it as a tumor composed of cells of the granulocytic series. Most of these are chloromas, others fail to exhibit the green color. I prefer the term 'granulocytic sarcoma' for all granulocytic tumors regardless of color. The hematologic picture of granulocytic leukemia, usually acute, should appear within not more than one year."

There was no recurrence of the lesion of the eyelid until February, 1964, when there was also proptosis and a paralysis of the left sixth cranial nerve with diminution of visual acuity to 20/50. The bone marrow was found normal again but showing signs of hyperplasia and a left shift in myeloid cells. The patient had a temporal decompression and was treated with 6 MP. In September, 1964, the patient was asymptomatic; the WBC was 6,000 cells and there were some atypical "monocytes" in circulation. In December, 1964, there were signs of orbital recurrence with added hearing loss. Irradiation with Cobalt-60 revealed definite radiosensitivity and resulted in decompression and regression of the mass. He was changed to methotraxate and, in April, 1965, he was again irradiated, given prednisone and antibiotics. The bone marrow was found again normal but with some atypical lymphocytes and monocytes. The patient was irradiated for palliation on the dorsal and lumbar spine, gradually declined and expired on November 9th, 1965.

Autopsy revealed the presence of homogeneous greenish intracranial masses attached to the inner surface of the dura; the largest of these masses was 8 cm in the left occipital region (Fig. 3).

Fig. 4—The tumor is composed of cells of the granulocytic series. Some of them contain coarse granules; these cells are eosinophilic myelocytes. The other cells with similar nuclear structures are myelocytes in which granules are not evident. This is probably attributable to the fact that neutrophilic granules are not readily seen in tissue sections and basophilic granules are dissolved in aqueous fixatives. (H & E x 1500)

Dr. Regato: Would it be unfair to point out the fact that pathologists might find all varieties of different maturations of lymphoid cells in the same slides? Eleven saw histiocytic; 6 were reticular; 2 were lymphoblastic; 5 were lymphocytic.

Dr. Rappaport: I will not comment unfavorably on anything pathologists do.

Dr. Steinfeld: It would be useful to know whether or not marrow aspirations were done subsequently to February, 1964, and whether or not they showed tumor cells; whether there was hepatomegaly, splenomegaly, weight loss, and what effect the drug therapy which was instituted had on the course of the disease. In retrospect, it would probably have been desirable to have been more aggressive locally in the absence of any real evidence of dissemination or systemic involvement by this tumor.

William T. Snoddy, M.D., Oklahoma City, Okla.: I submitted this case. Dr. John Devore, hematologist, was following the patient and he really had determined that this was granulocytic leukemia during the process of treatment.

Dr. Regato: That is correct, Dr. Snoddy. I failed to mention the fact that your hematologist had already made a diagnosis before the A.F.I.P. was consulted.

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2. Malignant Lymphoma (Histiocytic Type) of the Lung

Contributed by W. J. Frable, M.D.

Richmond, Virginia

THE PATIENT was a 73-year old woman in October, 1962, when she complained of diarrhea, pollakiuria and mid-abdominal pain spreading to the right lower quadrant. Physical findings suggested an acute appendicitis.

Dr. Mellins: There is a slightly lobulated, somewhat rounded soft tissue mass measuring 5.5cm in diameter projected over the lower half of the right lung field; the remainder of both lung fields is clear. The domes of the diaphragm are at normal levels. Heart size is at the upper limits of the normal and there is a decided unrolling of the aorta which may be a normal finding at this age.

The presence of acute inflammatory symptoms in the right lower quadrant together with a poorly defined mass in the thorax suggests the possibility of a pulmonary embolus. Absence of plate-like atelectasis, splinting of the right dome of the diaphragm, right pleural effusion and oligemia of other portions of the right lung tend to speak against this diagnosis. A primary pulmonary neoplasm cannot be excluded but it would be difficult to associate this with the clinical history. In 5% of all lymphosarcomas the first manifestation is in the gastrointestinal tract and the ileum is more frequently involved than the jejunum. Lymphosarcoma restricted to the appendix has been described. While the ordinary form of lymphosarcoma does not often involve the lungs, reticulum-cell sarcoma affects the lungs rather frequently and may produce large nodular masses. Lymphosarcoma may lead to early penetration or perforation of the intestinal wall, thus producing the symptoms of right lower quadrant pain, diarrhea, and frequency without dysuria.

Dr. Mellins' impression: LYMPHOSARCOMA, reticulum-cell type involving the terminal ileum or appendix with metastasis to the right lung.

Roentgenologic Impressions Submitted by Mail

Carcinoid	25
Carcinoma of colon with metastasis	23
Hodgkin's disease	16
Lymphosarcoma	23
Others	35

Dr. Mellins: I would think that, firstly, carcinoma of the colon does not metastasize to the lungs as a common or early complication; and, secondly, to make a diagnosis of metastasis, it is more convenient to have more than one single lesion. But I do not know that one could exclude this diagnosis. Usually, Hodgkin's disease is a desmoplastic reaction in the intestinal tract and obstruction is more likely to be the symptom with Hodgkin's disease in the intestinal tract. Lymphosarcoma is the diagnosis that I favor, and I suggest that it is of the reticulum-cell type because of the appearance of the lung nodule.

Dr. Regato: Dr. Benjamin Felson, of Cincinnati, offered an impression of carcinoid; Dr. J. W. Travis, of Topeka, suggested pulmonary lymphoma and Dr. R. Hill, of San Antonio, preferred Hodgkin's disease.

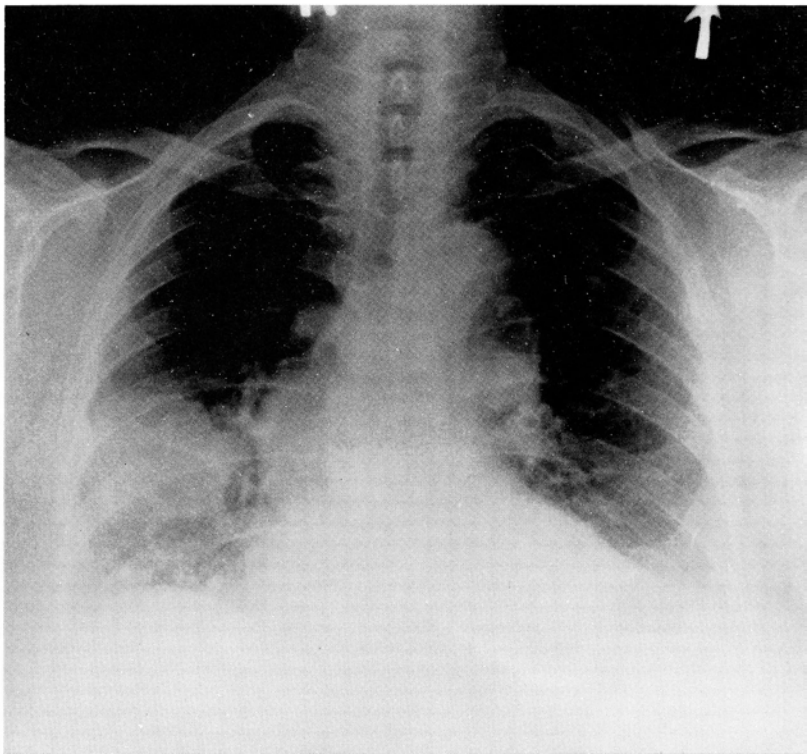
Operative findings: On October 2nd, 1962, an exploratory laparotomy revealed an acutely inflamed and perforated appendix with a carcinoid occupying much of the appendiceal lumen.

On December 12, 1962, a right sided thoracotomy was done with removal of the right upper and middle lobes. There was a firm, well delimited lesion, 5 cm in diameter, occupying the middle lobe and extending to the upper lobe; on cut section the mass was bright yellow, alternating with gray pink areas.

Dr. Rappaport: The sections of the lung show a pleomorphic cellular infiltration. As the term "pleomorphic" implies, there are cells of varying sizes and shapes. Two types of cells are represented here: 1) very large cells which I consider neoplastic histiocytes (so-called reticulum cells) and 2) small, fairly mature lymphocytes. In some areas, the neoplastic histiocytes predominate and the lymphocytes are scarce (Fig. 2). Mitotic figures are fairly abundant with up to 3 mitoses per high power field. I interpret this lesion as a malignant lymphoma, histiocytic type (reticulum-cell sarcoma).

The massive necrosis in this tumor is probably caused by arterial thrombosis; a thrombosed artery is evident near the margin of the necrotic area. Whether or not this is related to the abdominal operation, I am unable to tell. At the margins of the area of necrosis and even more distant from it, there was, also, an occlusive angiitis involving the smaller branches of bronchial arteries. However, the cells infiltrating the vessels and the perivascular tissue were lymphocytes and some histiocytes, none of which appeared cytologically malignant. This finding concerned me because of a recent article by Carrington and Liebow, describing a peculiar "limited form of angiitis and granulomatosis" of the lung. We shall refer to this article again in the discussion of Case IV. However, in spite of these inflammatory vascular changes, I still believe that we are dealing here with a malignant lymphoma of the histiocytic type.

Fig. 1—Slightly lobulated soft tissue mass of the lower half of the right lung field.



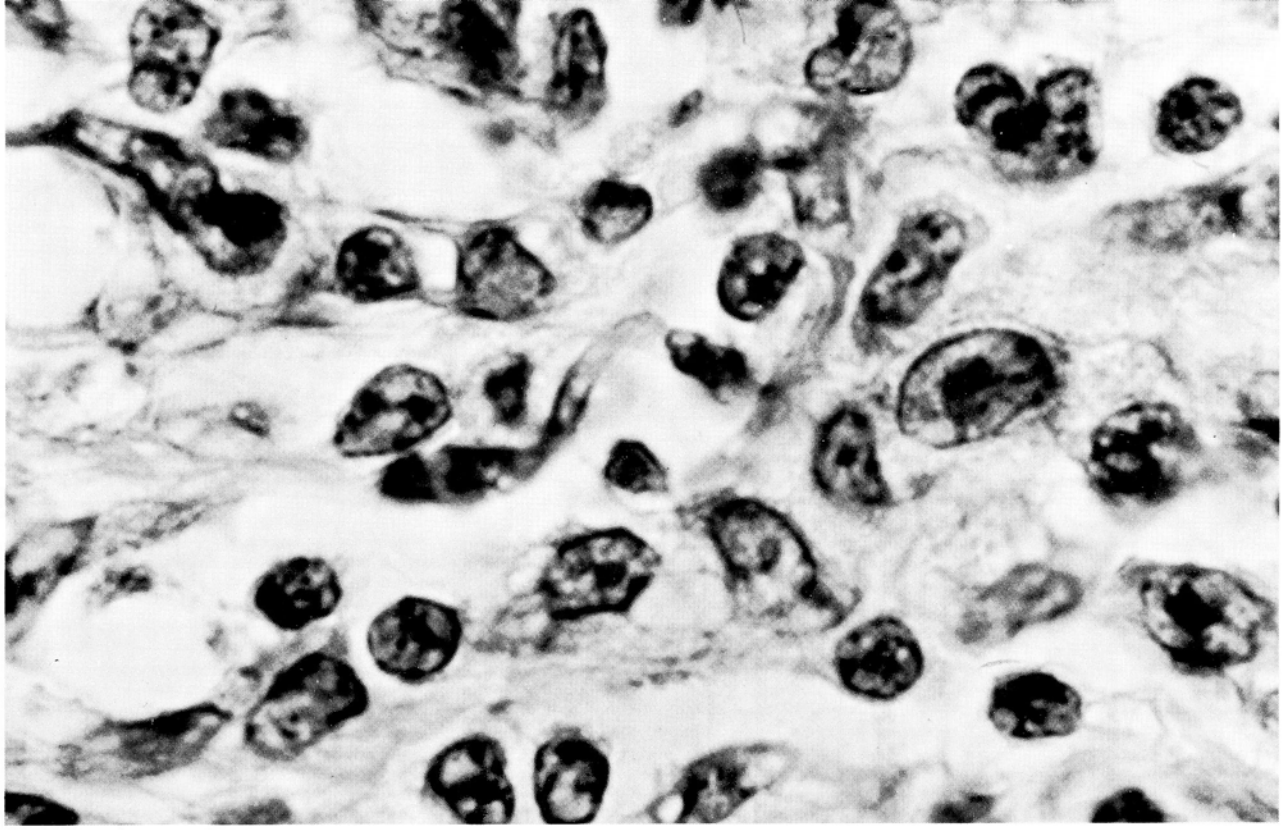


Fig. 2—The predominating cells of the pulmonary neoplasm are malignant histiocytes (reticulum cells). (H & E x 1500)

Dr. Rappaport's diagnosis: 1.) MALIGNANT LYMPHOMA, Histiocytic type (reticulum-cell sarcoma).

Histopathologic Diagnoses Submitted by Mail

Reticulum-cell sarcoma	58
Malignant lymphoma	21
Lymphosarcoma	10
*Hodgkin's disease	36
Carcinoma	25
Eleven others	34

Dr. Rappaport: It appears that the great majority of the group made the correct diagnosis. The 21 diagnoses of malignant lymphoma are also acceptable. I believe that the neoplastic element is not a lymphocyte but a histiocyte. Therefore, this is not a malignant lymphoma of the lymphocytic type. The diagnosis of Hodgkin's disease depends on one's criteria for diagnosing this disease: I could find no cells acceptable as Sternberg-Reed cells.

Dr. Regato: Dr. K. Hoffman, of Omaha, submitted a diagnosis of malignant lymphoma, *histiocytic* type; Dr. B. Peison, of Chicago, offered malignant lymphoma *reticulum-cell* type; Dr. W. Black, of St. Louis, preferred malignant lymphoma *lymphoblastic* type; Dr. Leo Lowbeer, of Tulsa, suggested malignant lymphoma *Hodgkin's type;* Dr. J. Kissane, of St. Louis, called it malignant lymphoma *mixed type.* Dr. A. O. Severance, of San Antonio, made a diagnosis of plain old lymphosarcoma.

Subsequent history: On February 6th, 1963, the patient expired following a hemiparesis which occurred suddenly: no evidence of residual tumor or any other neoplastic manifestation was found at autopsy.

Dr. Steinfeld: The carcinoid was apparently not a malignant tumor, but where two malignant tumors occur in the same patient, one of the most common, associated, malignant tumors, or two of them, are plasmacytic myeloma or multiple myeloma, lymphosarcoma or chronic lymphocytic leukemia. Both of these neoplasms of the hematopoietic system may be associated with hypo-gamma globulinemia, that is, normal gamma globulin. This is invariably the case in myeloma and occurs in 30 to 40% of patients with chronic lymphocytic leukemia. In both of these instances, this is due to failure of production of the globulin. I looked up one thing in reading these cases. I looked up pollakiuria and I thought that this patient probably had lymphosarcoma; frequently this is associated with hypercalcemia. The first symptoms the patient has are frequency of urination, ingestion of a lot of fluids, ultimately dry mouth and perhaps constipation and stupor. Diarrhea occurs occasionally in patients with malignant lymphoma as a result of extensive involvement of the mucus membrane and submucosa, and this is protein-losing enteropathy. There are other forms, such as intestinal lymphangiectasia, but in this kind of problem the patient has not only hypoalbuminemia and hypogamma globulinemia, but there is an increase in the production of the proteins. Here I do not think we have any evidence (certainly we have none at autopsy) that the patient had any tumor in areas other than those actually removed, but she did not survive very long after her thoracotomy. She had no flush, no asthma, and there was no mention made of 5-hydroxyindole-acetic-acid or catecholamines determination and this is all evidence, of course, against carcinoid with metastases and production of symptoms.

In the Annual Review of Medicine for 1965 there is an excellent review of endocrine manisfestations of non-endocrine tumors; it occupies forty or fifty pages and it is an excellent source of information (Bower).

Leo Lowbeer, M.D., Tulsa, Oklahoma: Doctor Mellins said that in Hodgkin's lymphoma of the small intestine, the first symptom is that of obstruction. On the contrary, sometimes the first symptom of a Hodgkin's lymphoma in the small intestine, particularly the jejunum, is that of perforation. I think Dr. Rappaport can bear me out on that, as there are a number of cases on record where this was the first manifestation of a malignant lymphoma of the Hodgkin's pattern in the jejunum, which, because of necrosis, led to a perforation peritonitis. We recently had occasion to see a case of this kind.

Dr. Mellins: I would agree that any of these lymphomas may perforate the bowel early. When one needs radiologically to differentiate between lymphomas as they affect the bowel, one finds that Hodgkin's disease produces narrowing whereas lymphosarcoma produces either an aneurysmal dilatation without obstruction, which may be characteristic and permit the diagnosis on that alone, or in 50% of cases nothing but a disordered motor pattern of the motility. I do not think that the two sets of remarks about Hodgkin's disease exclude one another; I think that one can get either perforation or narrowing.

I wonder if it is possible that the diagnosis of carcinoid might have been in error. Is it possible to confuse carcinoid cells with malignant lymphomatous cells?

Dr. Regato: There was no question about the diagnosis of carcinoid and the presence of a perforated appendix. The slide has been examined by Dr. Rappaport.

Dr. Rappaport: It showed unequivocal carcinoid.

Dr. Mellins: Well, on matters that are purple and pink, I must accede to Dr. Rappaport. Black and white is my domain!

Eugene C. Beatty, Jr., M.D., Denver, Colorado: You mentioned that no residual tumor was found at autopsy. How about the angiitis? Was it apparently localized to this lung lesion, or was it disseminated in other organs at autopsy?

Dr. Regato: Dr. Rappaport saw only the slides that you had and I do not have any other information in respect to residual findings.

Dr. Rappaport: I might say that the embolism, the thromboendartic phenomenon that I showed, may very well have been unrelated to the tumor but related to the patient's abdominal catastrophe from which he apparently died. It is also possible that the extent of necrosis may have provoked angiitis in the vicinity of this area and it may very well have been localized.

W. J. Frable, M.D., Richmond, Virginia: There was no other evidence of the angiitis in the autopsy.

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3. *Malignant (lymphocytic) Lymphoma (?) or Chronic Lymphogenous Leukemia (?)*

Contributed by H. W. Toll, Jr., M.D., Harold Palmer, M.D.

and P. K. Hamilton, Jr., M.D.

Denver, Colorado

THE PATIENT was a 40-year old woman in August, 1965, when she complained of a constant sensation of warmth, excessive perspiration and easy bruising; there was a history of "nephritis" and of tender cervical adenopathy in the past three years. Examination revealed small, freely-movable and non-tender nodes in the spinal and jugular chains and in the inguinal regions; the liver could be felt 3 cm below the costal margin; the spleen was also enlarged. There were 59% lymphocytes in the peripheral CBC; the hemoglobin was 12 gm % and the platelets were normal.

Dr. Mellins: There is slight widening of the superior mediastinum to the right. As seen through the cardiac silhouette, the paravertebral soft tissue mass appears widened. Except for an old healed fracture of the right clavicle, the chest film is otherwise normal. The plain roentgenogram of the abdomen reveals decided enlargement of the spleen; the lower pole of the spleen is at the level of the left iliac crest. The renal outlines are within the range of the normal in size. There is duplication of the left renal collecting system with displacement of the upper pole ureter laterally at the level of the lower collecting system; in all likelihood this is produced by a mass at the level of the hilus of the left kidney. The midportion of the right ureter appears to be displaced laterally. A portion of the left ureter is seen, crossing the sacrum; it is displaced medially and suggests a mass at the level of the left common iliac vessels. Periureteric fibrosis may result from lymphosarcoma. I exclude it in this case because there is no evidence of dilation of the ureters above the usual level of involvement, L5. The presence of enlarged para-aortic lymph nodes and a large spleen strongly suggests a lymphomatous disease. The differential diagnosis would seem to lie between lymphocytic lymphosarcoma and lymphatic leukemia.

Dr. Mellins' impression: 1.) LYMPHOCYTIC LYMPHOSARCOMA. 2.) LYMPHATIC LEUKEMIA.

Roentgenologic Impressions Submitted by Mail

Lymphoma	40
Chronic lymphatic leukemia	32
Hodgkin's disease	25
Others	31

Dr. Mellins: I would like to see more in the way of peritracheal and hilar node enlargement in the Hodgkin's disease. I have no way of excluding this disease, but it is not the usual presentation. I would say that it is either lymphocytic lymphosarcoma or lymphatic leukemia.

Dr. Regato: Dr. E. Salzman, of Denver, Dr. J. Cox, of Colorado Springs, Dr. T. A. J., resident at Jefferson Medical College, Philadelphia, and Dr. B. H. S., resident at Ann Arbor, offered an impression of chronic lymphogenous leukemia. Dr. R. J. Kurth, of Lackland Air Force Base, offered malignant lymphoma.

Operative findings: On August 24, 1965, an inguinal lymph node was removed for histologic examination.

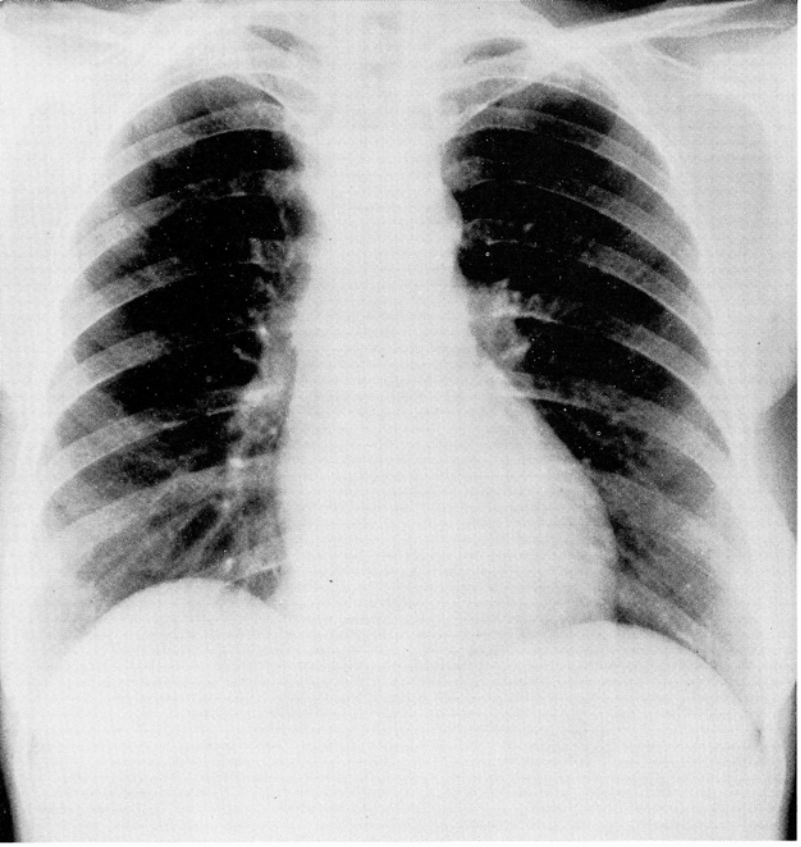

Fig. 1—Slight widening of the superior mediastinum to the right.

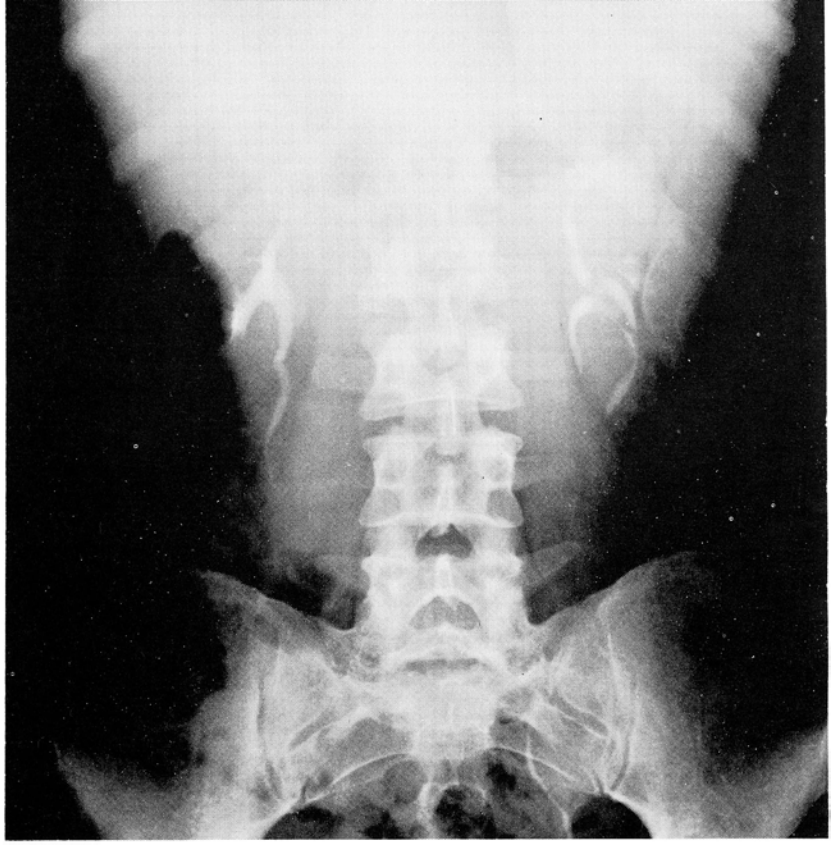

Fig. 2—Normal renal outlines; duplication of the left renal collecting system; enlargement of spleen.

Dr. Rappaport: There are cases of malignant disorders of the hematopoietic system in which the diagnosis is clear-cut from an examination of the histologic findings; there are instances in which hematologic information is helpful and others in which it is essential. In this case there were 59% lymphocytes in the peripheral blood; it is strange that we should be given this information without the total white blood cell count: fifty-nine per cent of 6,000 is within normal limits; 59% of 12,000 is a lymphocytosis.

The sections show an interesting feature, namely massive infiltration of the capsule and the pericapsular fat tissue (Fig. 3) without obliteration of the subcapsular sinuses. This phenomenon is attributable to obstruction of the lymph flow proximal to the lymph node under study. This being an inguinal lymph node, it is very likely that the obstruction was due to involvement of retroperitoneal nodes; this is a frequent occurrence in malignant lymphoma of inguinal lymph nodes and is often demonstrable by lymphangiography. Another interesting feature is the vaguely nodular pattern. Looking at the tumor cells at high magnification, marked variations in nuclear size and shape and heavy clumping of the nuclear chromatin (Fig. 4) are evident. It is really difficult to assess how much of this clumping is real and how much of it is artifact from delayed fixation; but a cellular pleomorphism, greater than that which occurs in chronic lymphocytic leukemia, is readily apparent. Dr. del Regato takes great delight in pointing out the variation in classification that pathologists offer when dealing with a malignant lymphoma. It is not easy to classify malignant lymphomas from tissue sections, but it is possible, provided certain technical precautions are taken: 1) lymph nodes should be cut as thin as possible; 2) they should not be placed into the fixative with the capsule intact; 3) they should not, if possible, be processed through the auto-technicon after only 6 to 12 hours of fixation; and, most importantly, 4) they should be treated with a certain amount of loving care.

In the differentiation of lymphocytic from histiocytic malignant lymphomas, it is often helpful to look for histiocytes in the same field for the purpose of comparing cell size. These can readily be found in malignant lymphocytic proliferations with the exception of chronic lymphocytic leukemia, where they are usually scarce. Since we have a good memory for shape, but a bad memory for size, and magnification plays such an important role in the study of histologic sections, it is always good to compare the average size of the predominating proliferating cell with the size of one or several histiocytes. If the predominating tumor cells are smaller, then you know you are dealing with a lymphocytic malignancy. If they are in the size range of non-neoplastic histiocytes then you know that you are dealing with a histiocytic, or, occasionally, with an undifferentiated (stem cell) type of malignant lymphoma. A feature that is important in differentiating chronic lymphocytic leukemia in tissue sections from lymphosarcoma is the usual absence or scarcity of mitoses in the former. Another point that I should like to bring out is that in many malignant lymphomas of the poorly differentiated lymphocytic type (i. e. lymphosarcoma), you will find a vaguely nodular pattern; this pattern is invariably accentuated by reticulin stains. Then, you may be faced with the problem of whether or not it is a so-called follicular lymphoma. This dilemma can be avoided by simply using the cytologic designation "malignant lymphoma, poorly differentiated lymphocytic type", and adding the term "nodular" if this is warranted by the architectural pattern. When the nodular formations are vague and indistinct, you might as well not add it, but this is often a matter of personal preference.

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA; poorly differentiated lymphocytic type (lymphosarcoma).

Histopathologic Diagnoses Submitted by Mail

Malignant lymphoma	92
histiocytic	5
reticular	18
lymphoblastic	40
lymphocytic	21
Lymphosarcoma	42
Follicular lymphoma	31
Lymphatic leukemia	25
*Hodgkin's disease	2
Other	5

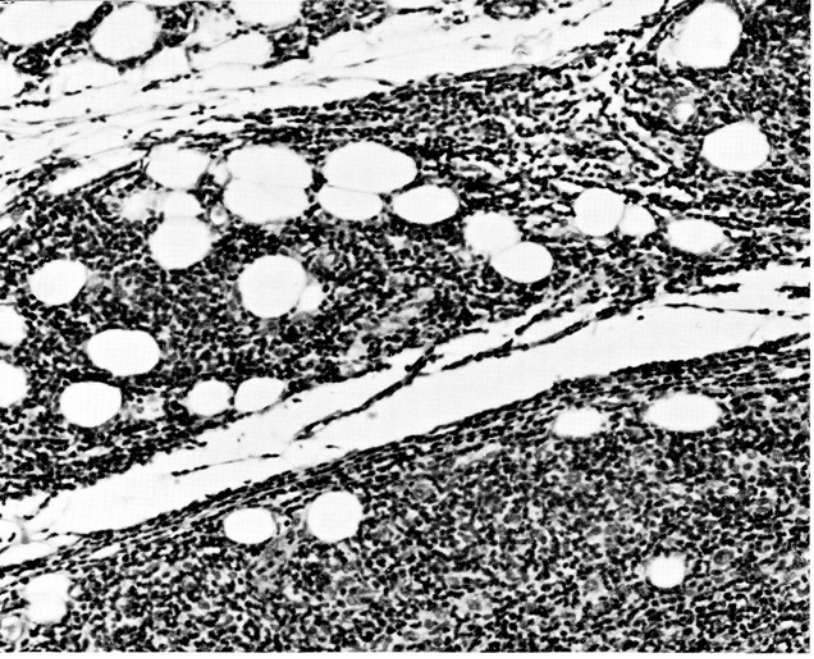

Fig. 3—A massive cellular infiltration is evident in the pericapsular fat tissue. (H & E x 250)

Dr. Rappaport: The terms "histiocytic" and "reticular", are used synonymously; therefore, differences in the tabulated diagnoses do not necessarily reflect differences in interpretation, but may indicate differences in nomenclature. We shall discuss the use of the terms "lymphoblastic" and "lymphocytic" in a moment. Lymphosarcoma is perfectly acceptable. Follicular lymphoma is a diagnosis made by those who were more impressed with the architectural pattern than with the cytologic features of this tumor. Lymphatic leukemia is a diagnosis difficult to make from the available sections; moreover, the term "lymphatic leukemia" is an insufficient and meaningless term: one should diagnose either "chronic lymphocytic leukemia" or "acute lymphoblastic leukemia", or "leukemic lymphosarcoma".

The diagnosis of Hodgkin's disease is not justified since Sternberg-Reed cells are lacking and the lymphocytic component is poorly differentiated, not mature, as in Hodgkin's disease. The difference between lymphocytic and so-called lymphoblastic (poorly differentiated lymphocytic) lymphomas are best appreciated when they are viewed simultaneously, as in this slide. If you do that, the uniformity of the well differentiated form and the moderate to marked cellular pleomorphism of the poorly differentiated lymphocytic lymphoma are readily apparent. When one makes a diagnosis of malignant lymphoma, well-differentiated lymphocytic type, it is done with the understanding that this is, in most instances, the tissue manifestation of chronic lymphocytic leukemia. But since we often do not have the hematologic data, we report it as "malignant lymphoma, well-differentiated lymphocytic type, consistent with chronic lymphocytic leukemia". On the other hand, the histologic diagnosis of malignant lymphoma of the poorly differentiated lymphocytic type is equivalent to the diagnosis of "lymphosarcoma", regardless of whether or not the patient has neoplastic cells in the peripheral blood. The same cytologic differences are evident in the blood. Mature appearing, well-differentiated lymphocytes in the peripheral blood that are characteristic of chronic lymphocytic leukemia are morphologically indistinguishable from normal circulating lymphocytes. Atypical lymphocytic cells with nuclear chromatin that is coarser than that of lymphoblasts, but not as heavily clumped as that of mature lymphocytes, and with nucleoli that have distinct and thick perinuclear rims, are characteristic of circulating lymphosarcoma cells. This was described by Dr. Raphael Isaacs in his classical paper on lymphosarcoma cell leukemia.

Infiltration of the bone marrow, per se, is not sufficient for the diagnosis of leukemia in the presence of an established diagnosis of poorly differentiated lymphocytic lymphoma or lymphosarcoma. It may merely mean diffuse infiltration of the bone marrow by tumor cells. One of the classical instances of a solid non-leukemic tumor of the lymphoreticular system is the so-called Burkitt's tumor. The bone marrow of patients with this tumor may, on occasion, become rapidly infiltrated by tumor cells, yet no one calls this disease a leukemia.

Some use the term "leukemia" to refer to the presence of abnormal cells in the blood; others use it to designate a specific disease entity, such as chronic granulocytic, chronic lymphocytic, acute lymphoblastic or acute myeloblastic leukemia. I believe it is well to differentiate between the proliferative hematopoietic disorders that appear to be systemic from their inception, at least clinically, and in which a leukemic blood picture represents the prevalent pattern of the disease, from those that usually begin with nodal or extranodal tumefaction and in which a leukemic blood picture is incidental, occurs in a minority of cases and often only in the terminal phases of the disease. In other words, we should not talk about leukemia merely as a state of the blood. We should always refer to a specific type of leukemia because only by being consistent in this respect will we learn more about the natural history of these diseases and, perhaps about their specific responses to therapy.

Dr. Regato: Dr. R. Delcourt, of Brussels, and Dr. Asa Barnes, of Washington, D. C., offered follicular lymphoma; Dr. H. A. Oberman, of Ann Arbor, and Dr. D. C. Craig, of Denver, preferred reticulum-cell sarcoma; Dr. R. L. Font, of Washington, D. C., offered lymphoblastic lymphosarcoma, if chronic leukemia is ruled out by hematologic studies; Dr. C. J. Farinacci, of San Antonio, Dr. E. F. Geever, of New York, and Dr. D. L. Dawson, of Colorado Springs, made a diagnosis of chronic lymphogenous leukemia.

Subsequent history: The histopathologists' opinions rendered were divided from nodular lymphoblastoma, through follicular lymphoblastoma, to reactive hyperplasia. The bone marrow appeared completely replaced by lymphoid tissue, with dense sheets of immature lymphocytes and marked normoblastic erythroid hyperplasia. The patient was started on chlorambucil in August, 1965, and one year later she was reported as doing well, but receiving irradiation for enlarged mesenteric and para-aortic nodes, as well as splenomegaly; there had been no weight loss. She is now under the care of Dr. P. K. Hamilton, of Denver.

Dr. Regato: In some cases submitted to these CANCER SEMINARS, we sometimes have a lot of entirely irrelevant information that we could give you; of course, we suppress most of it; naturally, we are accused of withholding information. On the other hand, if we give the information, we may be introducing "red herrings". Let me give you a list of the "red herrings" that I eliminated in this case: the patient was born in Massachusetts, she had intermenstrual spotting for eight months, one sister had poliomyelitis, one brother, now 34, had Hodgkin's disease 14 years ago, the patient is well developed and unusually attractive, a biopsy was done in the inguinal region at the patient's request for esthetic reasons!

Dr. Rappaport: All I was asking for is the total blood count.

Dr. Regato : The total white cell count was 6,400 cells per cubic millimeter with 59% lymphocytes on August 23rd; on August 30th it was 5,400 white cells with 70% lymphocytes. We gave the one count that was taken at the time

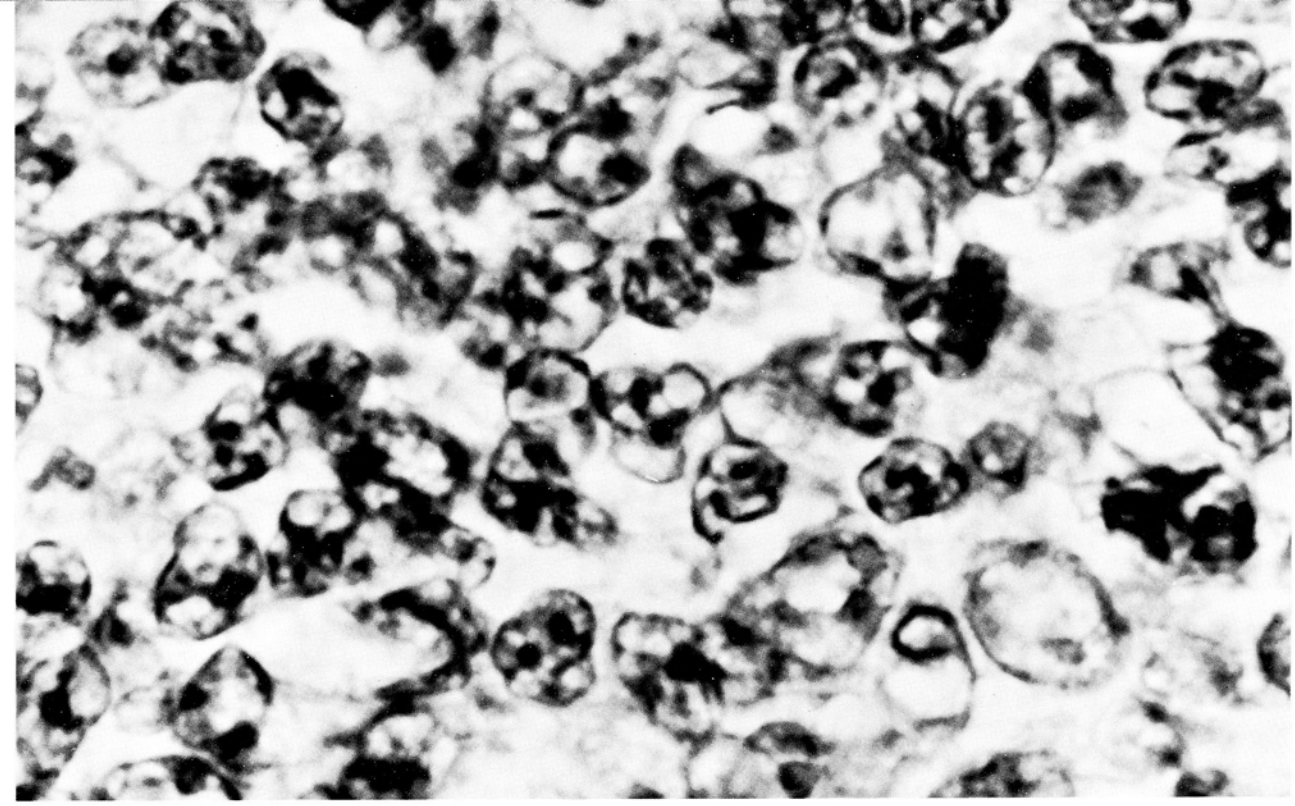

Fig. 4—The predominating cells are neoplastic lymphocytes. These cells are smaller than the histiocyte shown near the right lower corner of the illustration. Comparison of the predominating cell type with one or more histiocytes makes it possible to estimate cellular size, and to recognize the neoplastic cells as belonging to the lymphocytic series without regard to the magnification or the quality of the section. (H & E x 1500)

of the patient's first examination. She was also 5'4" in height and weighed 115 pounds.

Dr. Steinfeld: We want to know whether the white count is normal or elevated because 60 or 70% lymphocytes of a 3,000 white count means that the patient has a normal number of lymphocytes and actually has granulocytopenia; since she had been bruising and had been spotting, it probably would have been a good idea to see whether platelets were decreased; thrombocytopenic purpura is sometimes a harbinger of lymphoma.

Dr. Regato: The platelets were 103,000 per cubic millimeter; sedimentation rate, 14 mm per hour.

Dr. Steinfeld: This was probably not the basis of her bleeding. Easy bruisability, if it occurs within a relatively recent period of time after the patient gets sick, has much greater significance than if the patient has been bruising easily all her life. Patients with lymphoma may have symptoms of hemolytic anemia for a long time prior to the time that you can diagnose a lymphoma; they may have thrombocytopenic purpura for a period of time. A patient of ours, a man in his 70's presented with thrombocytopenic purpura. We treated him with steroids with no effect; we did a splenectomy with no effect; then we carefully followed him for several years with platelet counts and hemoglobin levels, and we found that the platelets were low and the hemoglobin was in the low normal range; finally we decided to do a white count and it was 60,000 with 95% lymphocytes and we had a diagnosis! Whenever a patient has thrombocytopenia, there is an absolute indication for a bone marrow aspiration to find out whether or not megakaryocytes are increased or decreased. In addition, in a patient who has this group of diseases (that is, lymphomas), we believe we should look very carefully at red cell morphology and do a reticulocyte count and a Coombs' test. A number of these patients have hemolytic anemia, whether Coombs' positive or not, and this makes a difference in treating them: if you treat them with alkylating agents, you may interrupt erythropoiesis in a patient who has a compensated hemolytic anemia. As part of the original workup, we should also have liver function tests, serum uric acid and a protein electrophoresis. These patients may come in with very high fever, quite ill, with a common organism (as pneumococcus), and if you know the patient is hypo-Gamma globulinemic, then is the time to give very large amounts of Gamma globulin. If the marrow shows diffuse replacement by lymphocytes: this is lymphocytic leukemia. Leukemia is a disease of the bone marrow, not of the blood: the patient may have more than 15,000 circulating cells, making it a leukemic leukemia; less than 15,000 circulating leukemic cells, making it subleukemic; or practically none, where we would say it is aleukemic. If there are enlarged lymph nodes, we would say that this is lymphosarcoma rather than leukemia, but I think this is a matter of semantics because our therapy is probably not going to vary; when we learn more about the etiology of these diseases, it will be important to have them classified a little more rigorously.

Now as for the therapy for this group of diseases, there are a number of treatments available. Irradiation of the spleen is an excellent form of treatment, even though the disease may be disseminated, because the lymphocyte is one cell which does leave its home, circulate in the blood, and then return to the lymph nodes and spleen; if one irradiates the spleen in a patient with chronic lymphocytic leukemia, lymph nodes very well may decrease in size all over the body. When one irradiates a fairly large volume of tissue in this disease, one is irradiating just about all of the lymphocytic tissue. So radiation therapy, whether given with ortho- or mega-voltage, or P-32, works very well. The alkylating agents also work well; agents such as Nitrogen mustard (probably not the best), Chlorambucil, Mitomycin C (which some might call an antibiotic: it is also an alkylating agent used in Japan) and Nitromin. Cychlophosphamide (Cytoxan) is an excellent alkylating agent; it causes much less thrombocytopenia than any other of the 1,200 alkylating agents which have been synthesized to date; its main serious side effect is alopecia. If one alkylating agent does not work in adequate dosage to

toxicity, no other will work. I do not know of any really proven case where a single alkylating agent carried to toxicity for a long time with failure was followed by successful administration of another alkylating agent.

Other agents that work include the corticosteroids. Unfortunately, these patients may have hypo-Gamma globulinemia and corticosteroids may interfere with their ability to respond to infection or make them more susceptible to infection. However, corticosteroids have a lymphocytolytic effect which may be utilized in the patient with marked granulocytopenia and thrombocytopenia. The Vinca alkyloids (Vinblastine and Vincristine) are occasionally used, although we would try to avoid them; there are experimental drugs which are useful when all else fails and these would include Streptonigrin and Methohydrazin.

Many patients with lymphomas have had large tumor masses for long periods of time and seem to live in happy symbiosis with their disease; aggressive therapy may cause them more trouble than help. I think one must let the punishment fit the crime and choose drugs for the patient; if the disease appears aggressive, one must be aggressive in therapy; if the disease is progressing slowly, one should be very gentle in therapy.

I certainly agree with the diagnosis; I think she has had a very good treatment and would anticipate that she would continue to do well for a fairly long period of time.

Dr. Rappaport: Dr. Steinfeld, with what diagnosis do you agree? Lymphosarcoma or lymphatic leukemia?

Dr. Steinfeld: I do not think it makes much difference which of these two you call it: if the disease was present in lymph nodes, I would say that this is lymphosarcoma; if lymphocytes were present, in sheets, in good sections of the marrow, I would say that this is lymphocytic leukemia. I do not think it makes much difference regarding therapy.

Dr. Rappaport: It may not make much difference as to the selection of treatment but it may make a great difference as to prognosis. Infiltration of the bone marrow, per se, is not sufficient for a diagnosis of leukemia in the presence of a diagnosed poorly differentiated lymphocytic lymphoma or lymphosarcoma. It may merely mean diffuse infiltration of the bone marrow by tumor cells. One of the classical instances of a solid tumor of the lymphoreticular system is the so-called Burkitt's tumor: the bone marrow becomes rapidly infiltrated by tumor cells, yet the tumor is treated like a solid tumor and not like a leukemia, although chemotherapeutic agents are being used for it.

Dr. Steinfeld: Regarding the Burkitt lymphoma, this is something which is unique. Primarily, though, it does not involve the marrow.

P. K. Hamilton, Jr., M. D., Denver, Colorado: There were lymphosarcoma cells in the peripheral blood initially, and these have persisted throughout the course of her disease in spite of therapy. She has done quite well in spite of therapy. She had Leukeran initially and, after less than 100 milligrams, developed a sudden neutropenia and leukopenia: the white cell count dropped to 2,000 and then to 800 cells per cubic centimeter. She has also had radiation therapy but no Cytoxan. She has lost no work since she was discharged from the hospital over a year ago.

Dr. Regato: Dr. Hamilton, you said that she had lymphosarcomatous cells in circulation. How do you define lymphosarcomatous cells in circulation? Is it written in the nucleoli?

Dr. Hamilton: They are large, lymphocytic cells with larger nuclei that are usually indented and have much finer chromatin than the normal lymphocyte.

H. Braunstein, M. D., Lexington, Kentucky: Did Dr. Rappaport imply that the mature lymphocytic type of lymphoma was invariably associated with chronic lymphocytic leukemia?

Dr. Rappaport: I did not say invariably. I said in most instances it is the histologic manisfestation of chronic lymphocytic leukemia, but since we cannot be certain from a tissue examination, we say: "malignant lymphoma, well differentiated, lymphocytic, consistent with chronic lymphocytic leukemia".

Dr. Regato: Permit me to clarify my often misconstrued position in this respect. I do not say that pathologists cannot tell the difference between a malignant tumor of the lymphoid series and leukemia in a lymph node. I do not contend that they should make the difference between one and the other, nor do I contend that they can. What I say is that we have numerous cases that, because they present with an enlarged lymph node, are first diagnosed as being a malignant tumor of the lymphoid structures and, subsequently, only because bone marrow biopsies are done, or because the disease shows in the peripheral blood, or the eventual picture is a clear one for acute or chronic leukemia, the patient is then diagnosed as having what he had in the first place. But, because another diagnosis had already been rendered, we whitewash this by saying that the malignant lymphoma became leukemia; all we have to do is to admit that we misdiagnosed leukemia as a malignant lymphoma to begin with. There is a great question and no particular scientific proof that these things become each other, but there is plenty of evidence that they can often become confused with each other; that is my contention, just a simple one. We agree with Dr. Rappaport that it does make a difference, because as soon as you make the diagnosis of a malignant tumor in these patients, they get the usual series of drugs, starting with the "drug du jour". This is dangerous to the patient's welfare for, if the patient has a chronic or subacute leukemia and precarious resistance, he might do better without any treatment.

Henry W. Toll, Jr., M. D., Denver, Colorado: Several questions were raised about this lady: the electrophoresis was normal, the serum uric acid was 9.3 mg % prior to the onset of treatment; the bone marrow showed the cells to be present in sheets. Dr. Amundsen, her first internist, had diagnosed this as a lymphoma prior to the biopsy, and Dr. Hammer called it a nodular lymphoblastoma from the roentgenograms prior to the histologic report. We called it a nodular lymphoblastoma. Several consultants thought it was lymphocytoma.

Dr. Rappaport: I believe it is well to differentiate between those disorders that appear to be systemic from the inception, at least clinically, and in which a leukemic blood picture represents the prevalent pattern of the disease, even though there are aleukemic instances. Those disorders that usually appear as a tumefaction and in which a leukemic blood picture is incidental, are only a minority of cases and sometimes this occurs only in the terminal phase of the disease. We should not talk about leukemia merely as a state of the blood and we should not lump them all together merely because of the presence of cells in the peripheral blood. We should speak of leukemia specifically designating the type because only then will we learn the natural history of the disease and the response to therapy; if differences are not evident now they may become evident as we learn more about these diseases.

Dr. Regato: Conheim, in the Nineteenth Century, described clinical cases that presented with a tumefaction, which were diagnosed as malignant lymphomas of some

kind or other, and that eventually proved to be cases of leukemia. Unfortunately, Conheim called these cases "pseudo-leukemia"; he should have called them "pseudo-lymphosarcomas" or "pseudomalignant lymphomas". We often hear the accommodating argument that it makes no difference what we call it, that in the long run they all end badly and have the same generalization, including a blood picture of leukemia or an involvement of the bone marrow. It is seldom considered that patients with primary lymphosarcomas of the upper air passages are either cured by adequate irradiation or die of generalization of the disease; neither group shows any manifestation of leukemia during their life span.

Dr. Steinfeld: It is unusual for the uric acid to be elevated in chronic lymphocytic leukemia, usually a disease of slow progression, although very rarely this may become relatively acute or subacute with rapid progression. The uric acid is generally elevated in acute lymphoblastic leukemia of childhood; it may be elevated in chronic granulocytic leukemia and also in myeloid metaplasia. When therapy is started, particularly when the tumor is sensitive, such as lymphoblastic leukemia treated with corticosteroids, the patients may have their serum uric acids go up to 70, 80 or 90 mg %; they may have a very fine remission of their disease but die of urate nephropathy. There is a new drug which is a xanthinoxidase inhibitor; it is called Allopurinol. I think for any patient who has an elevated uric acid in whom you initiate therapy (this would hold true for radiotherapy to a large radiosensitive tumor), it probably is desirable to put the patient on Zyloprim. This inhibits the oxidation of hypoxanthine and the oxidation of xanthine to uric acid so that the patient puts out in the urine not only uric acid in small amounts, but xanthine and hypoxanthine, and the problem of urate nephropathy should disappear.

R. Dorfman, M. D., St. Louis, Missouri: It seems to me that Dr. Rappaport was not very impressed by the nodular pattern of this tumor. From the time that Dr. Rappaport surveyed the follicular lymphomas at the Armed Forces Institute of Pathology, some of my colleagues have had a tendency to disregard the significance of the nodular pattern. In my own study of 94 cases of nodular lymphoma I was able to subclassify these into the five types that Dr. Rappaport has mentioned. At the same time, I found that there was a lack of nodular tumors in malignant lymphomas in African patients; this work was done in South Africa. In Dr. Rappaport's series there were only a few Negro patients. There was an equal sex incidence in my study (Gall, Morrison and Scott); it seems to me that we do not understand why some malignant lymphomas have this nodular pattern. Some of them are associated with clinical manifestations such as lymphocytosis; they have been reported to be associated with an increased incidence of pleural effusions. It seems that if we do not really know why a tumor assumes a particular pattern, we should retain the term in order to classify these subsequent studies.

Dr. Rappaport: I agree with Dr. Dorfman; his argument is well taken. I think in this case the term "nodular" should be added to the cytologic diagnosis.

M. H. Block, M. D., Denver, Colorado: The only criterion of whether or not treatment is doing well by this lady is not whether the liver or spleen become smaller, but whether she lives longer and better. She is working and she has not missed any time from work; but we would also like to know whether or not her hemoglobin, which is only 12 grams %, has risen; has her platelet count, which was 100,000, risen? She had a neutropenia, and we know that, at least when she was given drugs at the beginning, she got much worse. It would seem to me that we cannot say that the treatment has done this lady any good; we can only say that we have almost killed her with treatment.

We never seem to get two hematologists who agree about anything, and it is also hard to get the hematologist and the pathologist to agree. Alexander Maximow gave his definition of a hematologist as a man who has looked at ten smears of the peripheral blood and has a new theory of the origin of the plasma cell. Dr. Bloom's definition is even better: he said a hematologist is a man who has never met a cell he could not identify.

Dr. Regato: You may add to that, that a hematologist is a man who calls all malignant tumors "solid tumors", which has led one of our secretaries to ask if there were liquid tumors!

Dr. Block: This lady does not have chronic lymphatic leukemia; in chronic lymphatic leukemia there is not only involvement of the marrow, but the cells are small and dark. This patient with the larger type of cell that was shown, with involvement of the bone marrow, has a rather poor prognosis; she is not going to die because she has large lymph nodes but rather because she cannot produce red cells, white cells and platelets. Eventually, within a term of two or three years, and not ten years, as is the case in chronic lymphatic leukemia, she will not have enough bone marrow to produce these cells; in addition, treatment with any type of mustard tends to produce an auto-immune hemolytic disease at a much higher incidence than if the patient is treated with steroids or left alone. It is important to realize that unless the patient has normal globulins, she should not be vaccinated, because she is very prone to develop a systemic vaccinial reaction. It is extremely important not only to measure the serum uric acid, but also to measure the urinary uric acid; if the patient has a normal serum uric acid, this may mean that the turnover is normal or that the patient is excreting the large amounts of uric acid formed, through the kidneys; the reason the patient gets into trouble most of the time is not because of the serum but because of the urinary uric acid, particularly when treated with mustards; there is very often an increased breakdown of cells and a sudden increase in excretion of urates, so that the patient must be kept on a very high fluid diet. The prognosis in this case is not that of chronic lymphatic leukemia but that of a lymphoma which is involving the marrow; if she lives another two or three years, enough of the cells will spill out to the peripheral blood so that we will have to say that the patient is leukemic. Biologically, it does not make a bit of difference whether the cells live out their life span in the blood forming tissues without entering the blood, or whether they spill into the blood because there is a lot more leukemic tissue or abnormal tissue in the marrow.

Dr. Steinfeld: You cannot tell how aggressive a disease is unless you watch the patient for awhile; if this patient came in with sheets of lymphocytes in the marrow and with symptoms of hypermetabolism, she had to be treated. We have used alkylating agents (either Cychlophosphamide or Leukeran) in relatively low doses to begin with, in a fairly large number of patients. About half of the patients will have a fall in hemoglobin while on therapy. When one discontinues therapy the hemoglobin then will rise 1, 2, or 3 gm % above the pretreatment level, and as high as 6 or 7 gm % above nadir which occurred while on treatment. There is a small group of patients, in whom one is successful in guessing the dose of drug which will interrupt or destroy lymphocytes without interfering with erythropoiesis and whose hemoglobin will actually have a rise while on therapy; there are patients, of course, who get no benefit. We do not want to hurt these people; on the other hand, lymphocytic leukemia with replacement of the marrow is

not a benign disease. The benign disease is the one which occurs in the elderly man who has had lymph nodes in his neck for a long time; these are the patients that we watch or treat very, very gently. The patient who is symptomatic is going to require therapy and it should be judicious.

I think corticosteroids are not a primary form of therapy in this disease unless the patient has extensive marrow replacement, anemia and thrombocytopenia; the steroids are secondary to irradiation and alkylating agents; they do work but they cause many problems.

Editor's Note: This patient was last seen by Dr. Paul K. Hamilton in the beginning of July, 1967; she is in excellent general condition, has had discrete generalized adenopathy for which she has been given cortico-steroids. She is receiving no other therapy.

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4. Inflammatory Tumor (?) or Wegener's Granulomatosis of the Lung

Contributed by D. L. Bowerman, M. D.

Colorado Springs, Colorado

THE PATIENT was a 67-year old man in February, 1960, when he complained of malaise, fever, 25 pounds weight loss, cough and expectoration. On examination, the liver was questionably enlarged and there was no palpable adenopathy. The serum proteins, prothrombin time and urine were normal; there were 7,950 WBC per mm³ with 7% lymphocytes; the sputum was negative for acid fast bacilli.

Dr. Mellins: There is a homogeneous density occupying most of the lower 2/3rds of the left lung field, except for the costophrenic angle. It does not obliterate the shadow of the left heart border, indicating that it is within the lower lobe. A smaller similar density with a curved upper border is projected just above the midportion of the right dome of the diaphragm. A third small soft tissue density is seen in the anterior segment of the right upper lobe abutting against the horizontal fissure. There is no definite evidence of involvement of the lung roots. The remainder of the chest film is normal.

The chronicity of the disease and the lack of signs of acute inflammation would tend to exclude a bilateral pneumonia. The bilaterality and the presence of expectoration in an older man with chronic disease suggests the possibility of alveolar cell carcinoma. Alveolar Hodgkin's disease can give this appearance. It may be extensive and bilateral. It is not associated with bronchial obstruction. Fungus disease may be a superimposed inflammation in patients with lymphoma. It is usually more patchy in character and more disseminated.

Dr. Mellins' impression: HODGKIN'S DISEASE.

Roentgenologic Impressions Submitted by Mail

Hodgkin's disease	33
Alveolar-cell carcinoma	20
Lymphosarcoma	23
Leukemia	20
Others	31

Dr. Mellins: Certainly lymphosarcomas can give lung involvement but I have not seen as extensive a process as we see here in the left upper lobe, in lymphosarcoma. I would not be willing to exclude leukemia. The leukemias that we have seen give patchy infiltrated processes that may have fungus disease or moniliasis not uncommonly superimposed upon them; these likewise are patchy and not homogeneous. I think this is an alveolar lesion and one must consider Hodgkin's disease first, but I would not be able to exclude inflammatory pneumonia.

Dr. Regato: Dr. R. Hill, of San Antonio, and Dr. F. Wilson, of Colorado Springs, also submitted an impression of Hodgkin's disease; Dr. E. Salzman, of Denver, offered acute leukemia with bilateral pneumonia.

Operative findings: The patient was first subjected to treatment with antibiotics with some apparent improvement on the right lung lesions. On May 9th, 1960, a needle biopsy was done which was reported as showing malignant cells; this finding was followed by a left pneumonectomy. Two nodules, 3 cm and 4 cm in diameter, were found in the left lower lobe and a larger one, 11.5 cm, in the upper lobe; cut section of those masses showed muddy-gray areas of necrosis.

Dr. Rappaport: Histologic sections from this lesion show the interalveolar septa to be heavily infiltrated with cells, the type of which cannot be readily appreciated at this low magnification (Fig. 3). The pulmonary alveoli are filled with fibrinoid or necrotic material. Massive necrosis is evident in other areas. Masses of necrotic tissue also are present within bronchi. At a higher magnification a somewhat pleomorphic cellular population is evident (Fig. 4). Some cells are lymphocytes, some have peculiar indented nuclei and might be called monocytes and some can be identified as histiocytes. In areas one also sees an abundance of plasma cells, some of which contain Russell bodies. This explains why some of the pathologists have made the diagnosis of plasmacytoma. I interpret this as an inflammatory lesion. This is supported by the presence of severe occlusive angiitis next to the areas of necrosis (Figs. 5, 6). For a more specific interpretation of this inflammatory lesion, I requested the opinion of Dr. Liebow, who is a known authority on diseases of the lung. He wrote as follows:

> "We have encountered some thirty patients with somewhat similar lesions but composed predominantly of plasma cells which we have called 'plasma-cell granuloma'. These invariably proved to be benign and unassociated with dysproteinema. Many of these might

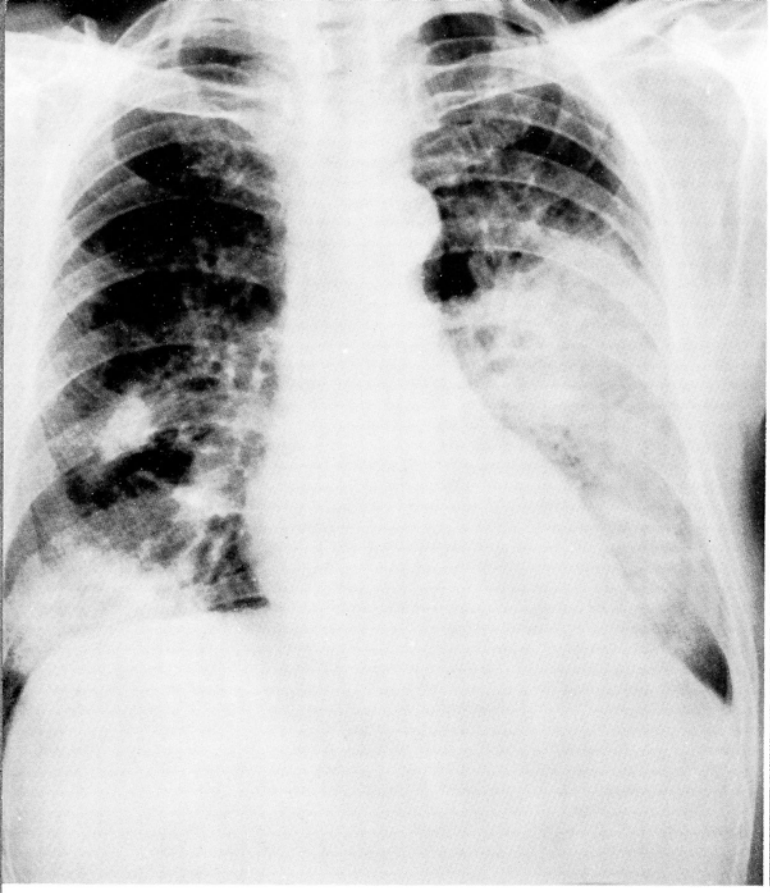

Fig. 1—Homogeneous density occupying most of the lower two-thirds of the left lung.

Fig. 2—Post-mortem appearance of the right lung showing edema and embolus.

be misdiagnosed as 'myelomas'. In our experience, they have invariably proved to be benign and have not recurred, even after limited resection. Some have occurred in quite young children. My conclusion is that your case represents a granulomatous and not a neoplastic process. Above all, Wegener's granulomatosis, especially of the limited type, is to be considered."

Dr. Liebow also commented on the fact that he has seen, in other cases, cells that resembled Sternberg-Reed cells.

Whatever this lesion is, it is not a malignant lymphoma but an inflammatory process and I would reserve judgment as to its precise position in the spectrum of inflammatory lesions of the lung. In their recent paper two characteristic features have been pointed out by Carrington and Liebow: (1) that the disease is invariably bilateral and (2) that an abundance of plasma cells is invariably observed.

Dr. Rappaport's diagnosis: INFLAMMATORY TUMOR OF LUNG with obliterative angiitis.

Histopathologic Diagnoses Submitted by Mail

*Hodgkin's disease	20
Chronic inflammation	19
Histiocytosis X	16
Blastomycosis	16
Malignant lymphoma	25
Pseudo-tumor	10
Plasma cell myeloma	15
Leukemia	8
Thirteen others	35

Dr. Rappaport: The diagnosis of Hodgkin's disease is understandable in the presence of a pleomorphic cellular population; however, this disease will be overdiagnosed unless one insists upon the presence of clear-cut Sternberg-Reed cells. Such cells were not evident in this lesion. Chronic inflammation is a correct diagnosis and so is inflammatory pseudo-tumor. I do not quite understand the diagnoses of histiocytosis X and blastomycosis. Plasma-cell myeloma is an extremely difficult diagnosis to make in extranodal location if the plasma cells are mature; I believe it is much safer not to make this diagnosis when the plasma cells lack features of neoplastic cells. One can find Russell bodies anywhere where plasma cells are abundant, but more often in inflammatory than in neoplastic lesions; Dr. A. P. Stout once commented to me that the presence of Russell bodies in plasma cells excludes their neoplastic nature. This has not been my experience, although it is perfectly true that Russell bodies are rarely evident in tissue sections of neoplastic lesions of plasma cells.

Dr. Regato: Dr. W. Black, of St. Louis, made a diagnosis of atypical pulmonary inflammatory infiltrate. Dr. E. Murphy, of Mexico City, and Dr. R. Nishiyama, of Ann Arbor, submitted a diagnosis of inflammatory pseudo-tumor; Dr. W. J. Frable, of Richmond, Virginia, offered plasma-cell granuloma. Dr. A. O. Severance, of San Antonio, wrote: "One thinks of plasmocytoma, reticulum-cell sarcoma and malignant histiocytosis: I chose the latter because I was convinced by my associates that these were not really plasma cells, that the variability of their size and elongated shape of some of them is more indicative of histiocytosis than of reticulum-cell sarcoma; but I would not be dogmatic."

Subsequent history: Histopathologic opinions were divided from organizing pneumonia through Hodgkin's to lymphosarcoma. Slides were submitted to the A.F.I.P. and Dr. S. H. Rosen rendered a diagnosis of malignant lymphoma, reticulum-cell type, with associated pneumonitis or possibly inflammatory pseudo-tumor or atypical Letterer-Siwe's (AFIP Accession No. 1052345). The process present in the right lung continued to clear under antibiotic therapy. In November, 1961, a mass was noted on the anterior abdominal wall; the patient was treated by roentgentherapy combined with nitrogen mustards with disappearance of the mass in the right lung. Residual lesions of the abdominal wall were excised and a diagnosis of granulomatous process was made. On February 29, 1964, the patient expired. An autopsy revealed bronchopneumonia of the right lung, an embolus of the trunk of the pulmonary artery and severe pulmonary edema.

Dr. Steinfeld: In a patient with plasma-cell or lymphocytic disease with an abnormal protein, immuno-electrophoresis will distinguish the I.C.G. from I.G.A. and I.G.M. The I.G.A. globulins or immuno-globulins A have about a 6% hexose content and the I.G.M. 10%; they are both PAS positive. But if one studies serum and urine in patients with this group of diseases, anywhere from 97 to 100% of cases will have an abnormal protein in either serum or urine. One can effectively rule out one of the lympho- or plasma-cell proliferative diseases associated with abnormal proteins. If we cannot be certain of the diagnosis and the patient is getting worse, we must confer very carefully with radiologists and pathologists. If the patient is not doing well, one should do a therapeutic trial on the basis of 1) the most likely diagnosis and 2) the type of therapy which would do the patient the least harm. In the absence of bacterial or fungal or other organisms, antibiotics certainly could be tried. In granulomatous disease, I would use corticosteroids if all the cultures were negative and the patient had an angiitis. In a patient where we have a question of a lymphoma, we probably would do a lymphangiogram; frequently, nodes, which we cannot palpate clinically, will show up. However, we have found tuberculosis on a lymphangiogram that we interpreted as Hodgkin's disease. If I were faced with this amount of information at this point with Dr. Rappaport's diagnosis, I probably would use corticosteroids and watch the patient very carefully; if he got worse, I would stop immediately.

D. L. Bowerman, M. D., Colorado Springs, Colorado: This was a joint endeavor on the part of Presbyterian and General Rose Memorial Hospitals of Denver; many attempts were made to recover organisms or to stain them in the tissue section. It is a relief to me, and I am sure it is to Dr. Toll, to hear Dr. Rappaport's comments this morning. We did sign this autopsy out as a granulomatosis involving primarily the pulmonary parenchyma but manifest in the subcutaneous nodules of the abdomen and the upper thighs. Dr. Helwig, of the A.F.I.P., suggested the diagnosis of an allergic type of granulomatosis because he had an opportunity to study the granulomatous lesions in the thigh. As to the serum proteins, they were normal and the spleen was not enlarged; this man died as a consequence of a massive pulmonary embolus.

Henry J. Caes, M. D., Sioux City, Iowa: If a thoracotomy was done, I would assume that a piece of tissue was sent to the pathologist for frozen section. What does Dr. Rappaport think about frozen sections in this group of diseases, in general, not only in the lymph nodes, but in such organs as the thyroid gland, lung and stomach; what is his experience with the cryostat or other forms of frozen sections?

Frank R. Dutra, M. D., Castro Valley, California: We have found it most useful, in making a rapid diagnosis on lymph nodes, to make an imprint which is stained with Giemsa simultaneously as we work with the cryotome; we actually get as much, or more, information, particularly in troublesome cases, from the study of the imprint than we do from the frozen section.

In regard to this particular case, it was noted, and apparently disregarded by some of the subsequent discussors, that a diagnosis of malignancy had been made from a needle biopsy of the lung. There is a recent paper (Carrington) in which a large series of biopsies of the lung with a needle were reported; the paper is extremely interesting. But the photographs that were used are not diagnostic in most cases; in reading the details of the protocols, the diagnoses actually submitted are generally and simply consistent with whatever the clinical diagnoses were.

Weldon K. Bullock, M. D., Los Angeles, California: The direct smear, not the imprint, is very valuable in the differentiation of carcinomas from lymphomas. With a scraped smear you get clumps of cohesive cells which you never get in a malignant lymphoma. However, there are three places where this may not serve: oat cell carcinoma of the lung, malignant neuroblastomas, and sometimes in melanomas. In regard to the cryostat frozen sections, we find it very difficult in retroperitoneal tumors to make a distinction from liposarcoma, for example, without a smear. We have been mistaken by reading the cryostat and calling it an undifferentiated liposarcoma, when on fixed paraffin sections it turned out to be a malignant lymphoma. So we try to have every frozen section accompanied by a direct scraped smear.

Robert M. Nalbandian, M. D., Royal Oak, Michigan: We, like Dr. Dutra, have used the procedure he outlined with great benefit for a number of years, but there is one caveat that should be offered on the interpretation of imprints: that you do get a selective population. You do not always get the cells in the same proportion, particularly with reference to the more immature cells, the reticulum cells: one might be misled if one placed too much reliance without that awareness.

Fig. 3—The pulmonary parenchyma at the margin of the lesion shows a heavy cellular infiltration of the interalveolar septa. (H & E x 250)

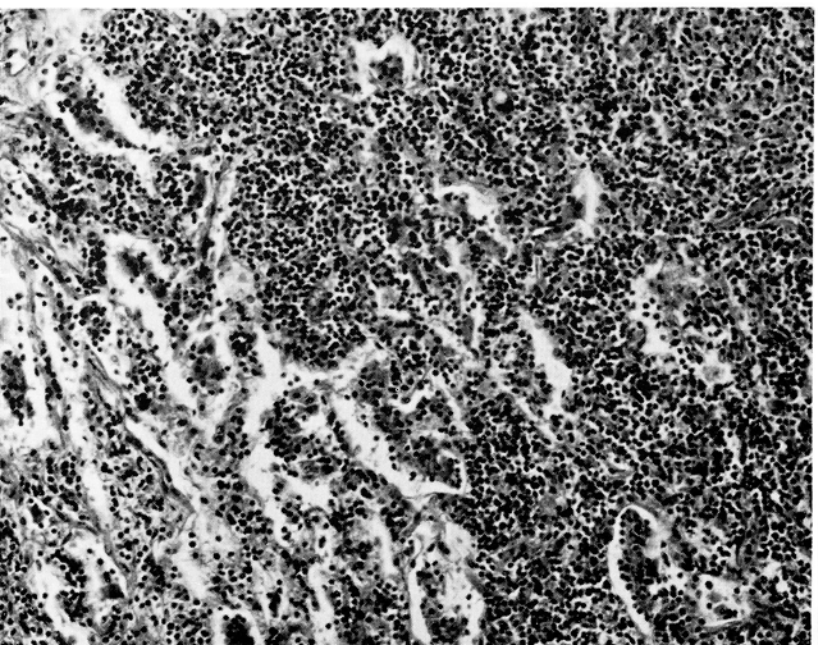

Fig. 4—In this area the cellular infiltrate is composed of histiocytes and plasma cells. (H & E x 1000)

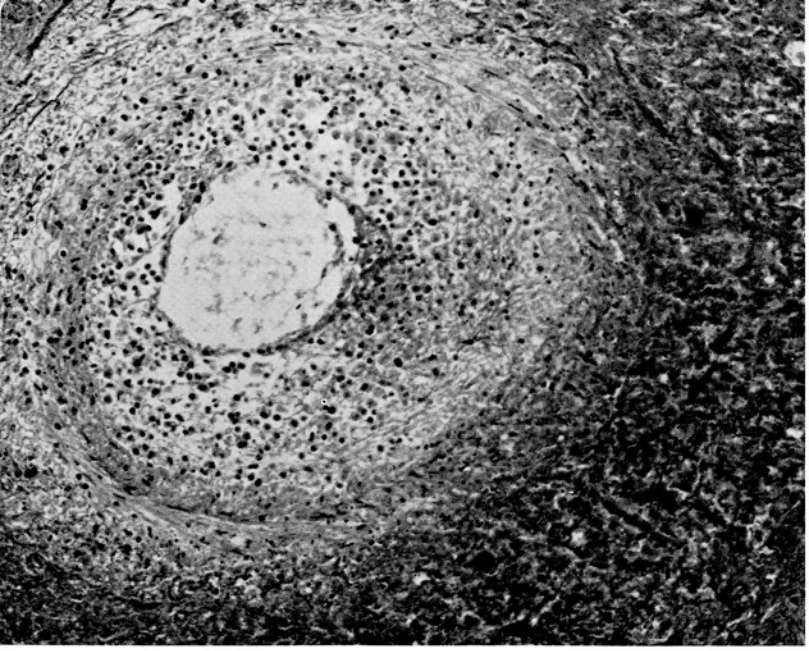

Fig. 5—At the margin of an area of necrosis an artery reveals marked infiltration of the intima with inflammatory cells. The necrosis has extended into the arterial wall. (H & E x 250)

Fig. 6—An elastica stain reveals a heavy infiltration of the intima of an artery; this has resulted in extreme narrowing of arterial lumen. (Elastica—van Gieson's stain x 250)

Marvin L. Daves, M. D., Denver, Colorado: I am just curious to hear the rationale of the pneumonectomy defended in this patient, since there was obvious disease in two lobes on the other side.

Leo Lowbeer, M. D., Tulsa, Oklahoma: I notice that this patient finally died with a pulmonary embolism. Is it not a possibility that the primary disease here consisted of small pulmonary emboli from the recognized thrombi of veins, or is it peculiar reaction to the infection this patient may have had? It is virtually impossible to distinguish between primary thrombosis of pulmonary arteries or small pulmonary arteries and secondary thrombosis secondary to small emboli.

Dr. Rappaport: I really do not want to comment on this because it is not subject to a decision on the basis of the material that we have.

John W. Pickren, M. D., Buffalo, New York: There is one thing that we saw in these slides that has not been commented upon. We placed this slide between the polarized lenses, crossed the beams, and found that there was a great starry appearance. There were large numbers of double refractile particles throughout, and these particles were prominent in the fibrinoid material that was present in the bronchi. I do not know whether this double refractile material is the cause of an inflammatory reaction or perhaps the result. We know that many of the bronchographic media that have been used in the past are double refractile and we also know that this bronchographic media will cause a severe pneumonitis of this type. I wonder if Dr. Rappaport did see these foreign bodies that are present in these sections and what his ideas are about them.

Dr. Rappaport: Did you take a photograph of this and bring it along for comment?

Dr. Pickren: I took a photograph, but unfortunately it has not been developed.

Dr. Rappaport: Well, I did not see it; I am embarrassed.

Capt. Michael M. O'Brien, M. C., Fort, Carson, Colorado: I just wanted to confirm that finding. We also found all these bodies, and they were double refractile; we did take a photograph but it is not back yet.

Dr. Rappaport: I am doubly embarrassed.

Dr. Dutra: Double refractile material resulting from bronchographic media instilled into the lung is very commonly seen in conditions where we have lung tissue to study; it will stay indefinitely, in areas of chronic inflammation. However, there is virtually no evidence to indicate that it is etiologic; we wrote a paper recently on this subject.

Dr. Mellins: I read in the protocol that in November a mass was noted in the anterior abdominal wall and the patient was treated by roentgentherapy with disappearance of the mass in the right lung. I do not know whether the mass disappeared because of, in spite of, or concomitant with the radiation therapy. At the autopsy no lesion was found in the right lung; this would tend to be against the diagnosis Wegener's granulomatosis.

Dr. Rappaport: It is very difficult for me to comment on what a frozen section in this particular case would have revealed. I doubt very much whether we would have been willing to commit ourselves on a frozen section of such a complex lesion. I am not prepared to defend the diagnosis of Wegener's granulomatosis. This was not my diagnosis; but I have a great deal of respect for Dr. Liebow's experience in this field. My own diagnosis, as I said, was inflammatory tumor with obliterative angiitis. I am going to stick to it.

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5. Mediastinal Lymph Node Hyperplasia

Contributed by R. LePere, M. D., G. Mani, M. D. and P. W. Voltz, Jr., M. D.

San Antonio, Texas

THE PATIENT was a 19-year old girl in October, 1961, when on a routine survey roentgenogram of the chest she was found to have a mass in the left paratracheal region. There were no abnormal physical or laboratory findings; bronchoscopy was negative.

Dr. Mellins: There is a mass arising in the superior mediastinum and extending to the left at the level of the aortic arch. It has a smooth, sharply-defined, curved lateral border and is approximately 2 centimeters in diameter. There is no evidence of calcification or cavitation within the soft tissue mass. Vertebral erosion or rib erosion are absent. The remainder of the chest film is normal.

In the presence of a mass in the mid-portion of the superior mediastinum in a young asymptomatic individual, further film studies would be necessary in order to make a radiographic diagnosis. A lateral chest film, a barium esophagram and selective arteriography might furnish identifying information. It is, of course, not uncommon, for a complete study of this kind to be nonrevealing and the diagnosis is not evident until exploratory operation and biopsy.

Of the malignant lesions, the commonest to present this way is a lymphoma which could be either Hodgkin's disease or lymphosarcoma, although it is more common for the former to be asymptomatic. An ectopic thyroid or a parathyroid gland may give this appearance but they are more commonly anterior and smaller. Paratracheal and paraesophageal cysts might cause a slight indentation of the barium filled esophagus. They are more common on the right than on the left. A well demarcated shadow in the paratracheal region may be produced by a neurilemoma of the vagus nerve. A tuberculous glandular lesion may exist with little or no clinical indication of the nature of the shadow.

Dr. Mellins' impression: 1.) BENIGN MIDDLE MEDIASTINAL TUMOR. 2.) HODGKIN'S DISEASE.

Roentgenologic Impressions Submitted by Mail

Thymoma	29
Hodgkin's disease	24
Malignant 'lymphoma'	13
Teratoma	8
Others, benign	38

Dr. Mellins: I cannot exclude thymoma; I would expect this to be in the anterior mediastinum rather than in the middle mediastinum, but it is possible to have it in the middle mediastinum; I think it is less common at this age and under these circumstances than Hodgkin's disease. About malignant lymphoma, again at nineteen years of age I would still lean away from some non-specific lesion presenting in this way and lean toward Hodgkin's. There is no radiographic, which is to say, there is no gross pathologic evidence to support teratoma. There is neither calcification, nor is there a fat fluid level which is produced in the upright film by the grumous material in teratoma. I, therefore, would say that the odds would favor a benign middle mediastinal lesion; if it is a malignant lesion, it is probably Hodgkin's disease.

Dr. Regato:. Dr. B. Felson, of Cincinnati, suggested a benign thymic lymphoma; Dr. J. T. McClintock, of Denver, offered giant follicular lymphoma; Dr. Neal Goodman, of Denver, preferred benign mediastinal lymphadenopathy; Dr. F. Wilson, of Colorado Springs, preferred to call it a hamartoma. Dr. Shu-Ren Lin, of Philadelphia, chose benign lymphoma.

Operative findings: On October 13th, 1961, a left lateral thoracotomy was done: an encapsulated subpleural mass, 5 x 4 x 4 cm was found lying over the origin of the subclavian artery. The mass was sharply dissected and resected.

Dr. Rappaport: This case represents a well known entity that has been described by Castleman and his associates under the term "mediastinal lymph node hyperplasia resembling thymoma". It is a lesion in which the usual architectural features of lymph node tissue cannot always be demonstrated. The lesion is characterized by widely separated follicle-like structures (Fig. 3), some of which have central areas of fibrosis. Many of them show vascularization of their centers. A marked fibrous reaction of the interfollicular tissue is often evident. The cellular components are primarily lymphocytes with an admixture of histiocytes; nodular areas composed of mature lymphocytes are also evident in some areas. Dr. Castleman has pointed out the relationship of these follicle-like structures with fine vascular twigs that approach them and sometimes penetrate into their center. Reticulin stains accentuate this feature (Fig. 4). Note also that even though the reticulin fibers are abundant around the follicles, they are not compressed at the margin, such as one often observes in malignant lymphomas with follicular patterns.

The reason why Dr. Castleman reported this lesion as mediastinal lymph node hyperplasia resembling thymoma, stems from the fact that small vessels with hyperplastic endothelial cells in the centers of the follicles have been confused with Hassall's bodies in the past. These lesions have been reported as "extrathymic thymoma" when they occurred in extramediastinal locations and as thymomas when they occurred in the anterior mediastinum. Unlike thymoma, this lesion is usually, but not always, asymmetrically located; while thymoma is usually in the center of the anterior mediastinum.

Dr. Rappaport's diagnosis: MEDIASTINAL LYMPH NODE HYPERPLASIA.

Histiopathologic Diagnoses Submitted by Mail

Lymphoid hyperplasia	101
Hamartoma	17
Thymoma	18
Lymphosarcoma	10
*Hodgkin's disease	5
Five others	12

Dr. Rappaport: This lesion was recognized and diagnosed correctly by the great majority of pathologists. The term hamartoma which appears in the list of diagnoses is the one that Dr. Lattes has proposed for these lesions. I do not believe that it is applicable. Other terms that have been used are angiofollicular lymph-node hyperplasia (Harrison) anl lymphoreticuloma (Zettergren).

Dr. Regato: The majority of the experts were agreed in a diagnosis of benign, pseudo-thymic, hamartomatous,

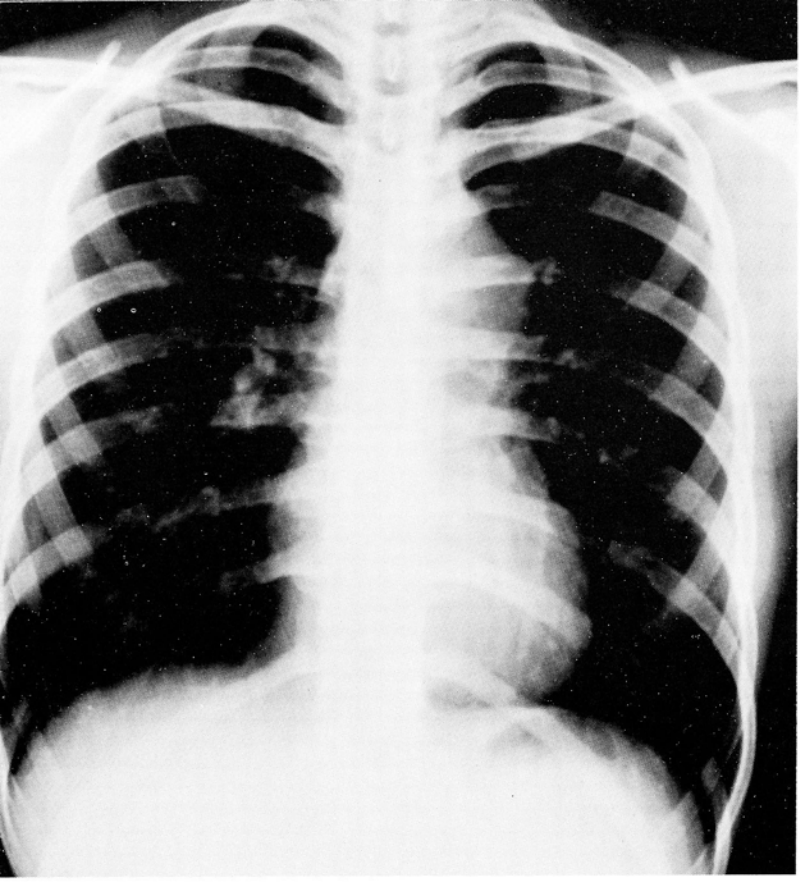


Fig. 1—Mass of the superior mediastinum extending to the left at the level of the aorta.

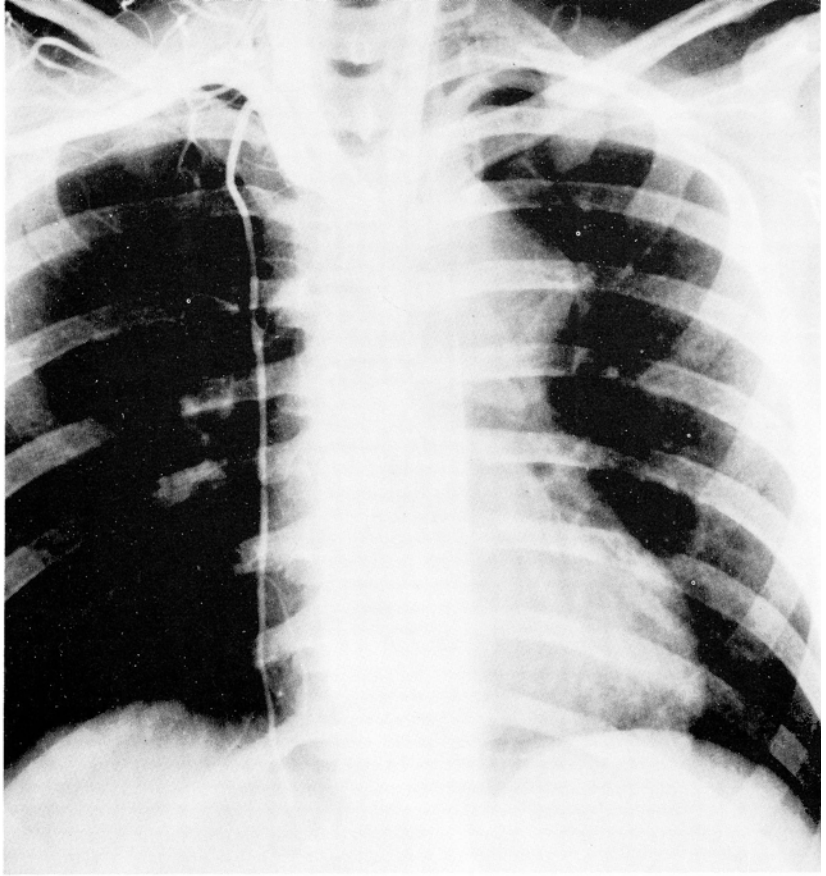


Fig. 2—Arteriogram shows only the left sided extension of the mass.

angiofollicular, reticular, lymphoid hyperplasia of the mediastinum, currently attributed to Castleman, Iverson and Pardo-Menéndez.

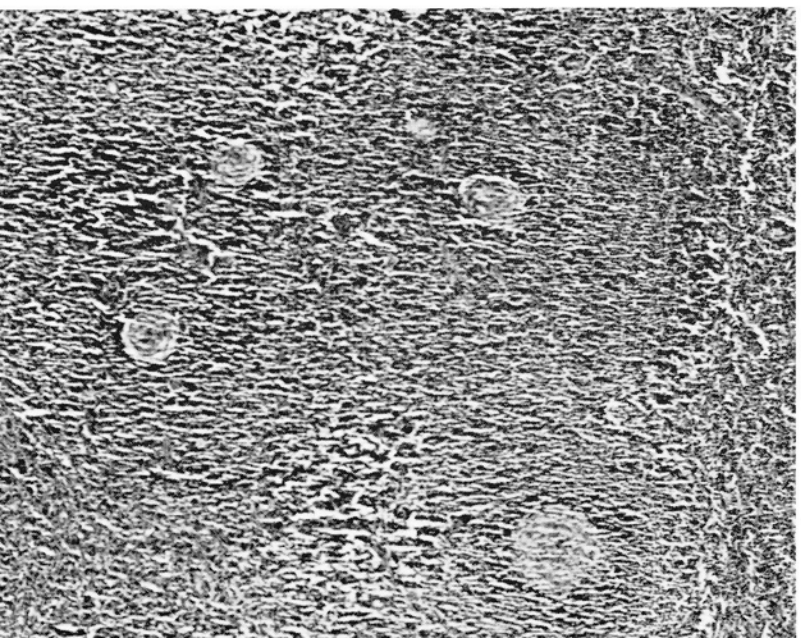
Subsequent history: In January, 1966, the patient had married and was reported in good health and entirely asymptomatic.

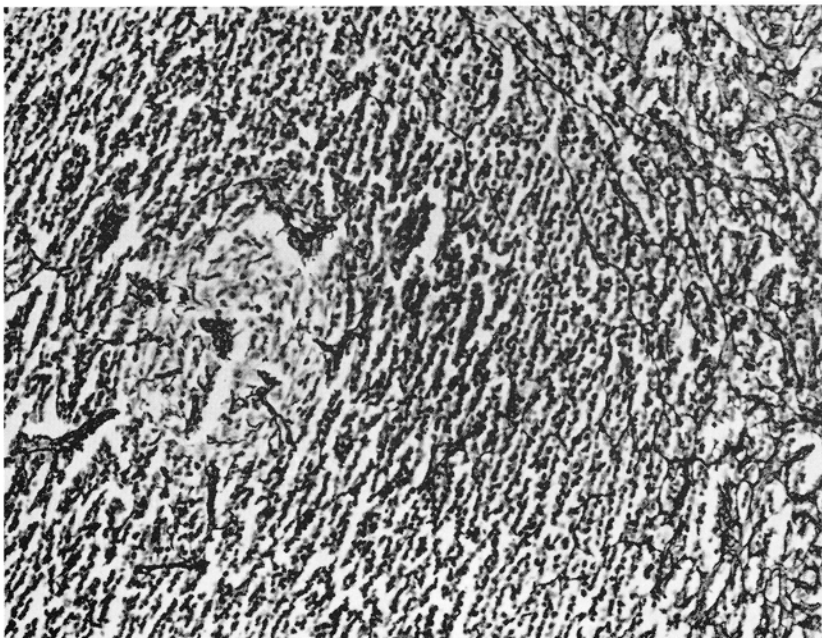
Murray R. Abell, M. D., Ann Arbor, Michigan: I have not had the experience of Dr. Lattes but we tend to favor his interpretation. We have a small group of twelve of these lesions and in four we can find residual lymphoid tissue along one pole; we view this as a tumor within a lymph node, at least in some situations. There is other evidence that some of these can be found outside of lymph nodes. The ones we have seen have been in children or young adults and of an average size of 6 or 7 cm in size; we view them in the nature of blastomatoid lesions or hamartomas of lymphoid tissue, some of which arise definitely in lymph nodes. We would have called this one a lymphoid hamartoma.

Dr. Steinfeld: This is easy in retrospect. If we are faced with the problem of a mass in the chest in a young girl, before opening her chest, we would probably do a whole series of examinations and among these blood counts, liver function tests, bone marrow, and probably lymphangiography. One would want to reassure the patient and her family that this is a benign condition, and in order to do this one would have to have fairly extensive studies.

Fig. 3—Mediastinal lymph node hyperplasia. Note the widely separated small follicles surrounded by a proliferation of small lymphocytes. (H & E x 125)

Fig. 4—Reticulin fibers are seen to penetrate into a small reaction center of a follicle. Some of the reticulin fibers accentuate the outlines of delicate vascular twigs. The reticulin fibers at the periphery of the follicle are abundant, but do not appear compressed. (Reticulin stain x 250)





Alvin O. Severance, M. D., San Antonio, Texas: Nothing has been said about location other than in the mediastinum but I am sure that these lesions have been reported elsewhere. My first experience with one was in the axilla and my most recent experience was in the thigh, not the groin, but down in the thigh which is an unusual location for a lesion of this type.

Dr. Rappaport: Yes, they have been reported in various locations and I have not mentioned all of them. I think your remarks are entirely correct.

Dr. Abell: I think the most common site is mediastinum or neck and next axilla, and then other unusual locations, such as skeletal muscle and subcutaneous tissue. I know of only two reports in the retroperitoneal space, but I have never seen one myself.

John W. Pickren, M. D., Buffalo, New York: Very recently, a young man who was having a pre-induction physical examination was found to have this lesion and he was referred to our hospital. This patient started oozing after the operation; he had a severe platelet depression. His platelet count prior to the operation was normal. I was wondering if anyone else had seen such a complication.

Ronald Dorfman, M. D., St. Louis, Missouri: We have had one lesion of this type in the subcutaneous tissues of the shoulder, and one in the broad ligament, which was misdiagnosed by a gynecological pathologist as follicular lymphoma. I would like to draw your attention to an article which I saw describing mediastinal lymph node hyperplasia in association with red cell aplasia, but unfortunately I have lost the reference.

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6. Lymphocytic Tumor of the Lung, benign (?) or Tumor-like Lymphocytic Pulmonary Infiltrate

Contributed by H. F. Elmendorf, M. D. and A. O. Severance, M. D.

San Antonio, Texas

THE PATIENT was a 54-year old man in December, 1965, when he complained of a feeling of "heaviness" in the right side of the chest; there was a history of "pneumonia" two years previously, but he presented no dyspnea, no cough, no fever and no weight loss. Bronchoscopy was negative.

Dr. Mellins: There is a non-homogeneous density which has an oblique inferior margin, situated in the right cardiophrenic angle and obliterating the right heart border. Lateral to it are many streaky densities which obliterate a portion of the outline of the right diaphragmatic dome. There is slight elevation of the right dome of the diaphragm and mild hyperlucency of the right midlung field as compared to the left. There is a suggestion of an air bronchogram within this area of consolidation, suggesting that the density is alveolar in character. A fairly well defined area of increased density is seen in the left posterior basal lung segment and there is a nodular density about 1 cm in diameter projected over the anterior portion of the left 5th rib. The lung roots and skeletal structures appear normal.

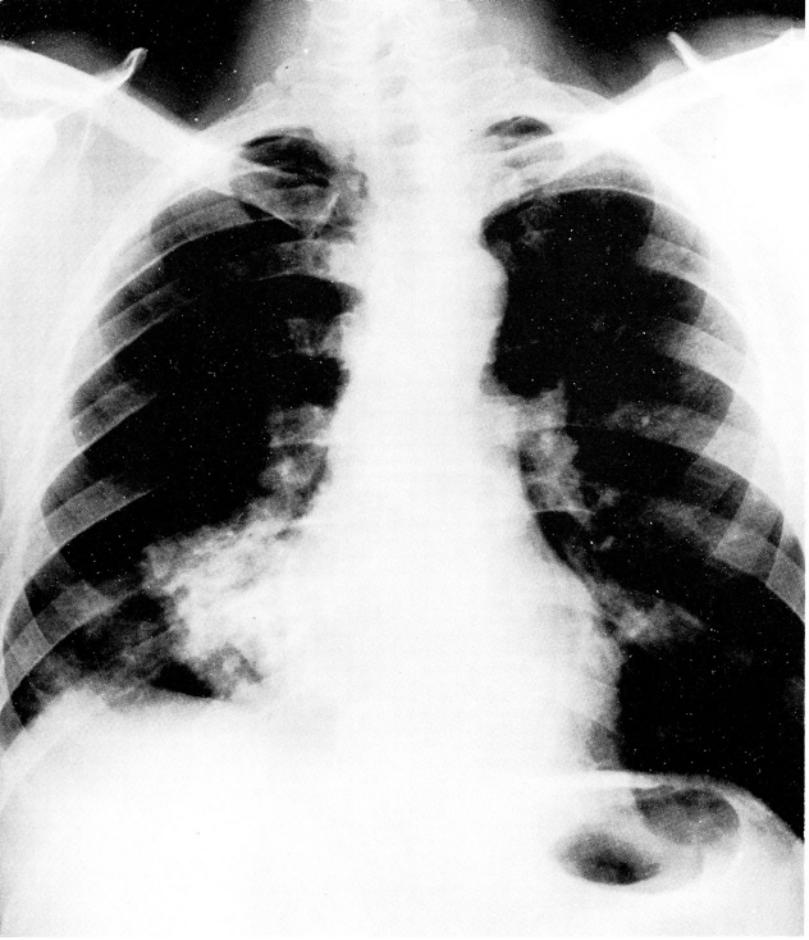
Because of non-homogeneous involvement of portions of both lung bases and the retractive process in the right middle lobe some form of organized pneumonitis must be strongly considered. Unresolved pneumonia may be the cause. Aspiration pneumonia may likewise organize. Lipoid pneumonia is unilateral or bilateral with about equal frequency. It may involve the middle lobe and it produces the picture of an organizing pneumonia, occasionally simulating a tumor.

Dr. Mellins' impression: ORGANIZING PNEUMONIA, right middle lobe.

Roentgenologic Impressions Submitted by Mail

Bronchial carcinoma	27
Middle lobe syndrome	25
Pulmonary lymphoma	21
Pseudolymphoma	8
Others	38

Dr. Mellins: The diagnosis of bronchial carcinoma is based upon the fact that there is middle lobe involvement with loss of lung volume; one would need to see evidence of the mass through some kind of bronchial study in order to make that diagnosis. Middle lobe syndrome is a fair diagnosis. It would not, however, account for the other changes that we see in the lung. It is generally produced by lymph node involvement of inflammatory nature in the mediastinum and it produces even more loss of volume than we have at the present time. Pulmonary lymphoma is difficult to accept on the basis of its non-homogeneous character. I assume that by "pseudolymphoma" is meant the lymphoid infiltrates that apparently follow viral infections; I would feel that something of this nature or an organizing pneumonia is the most likely possibility.



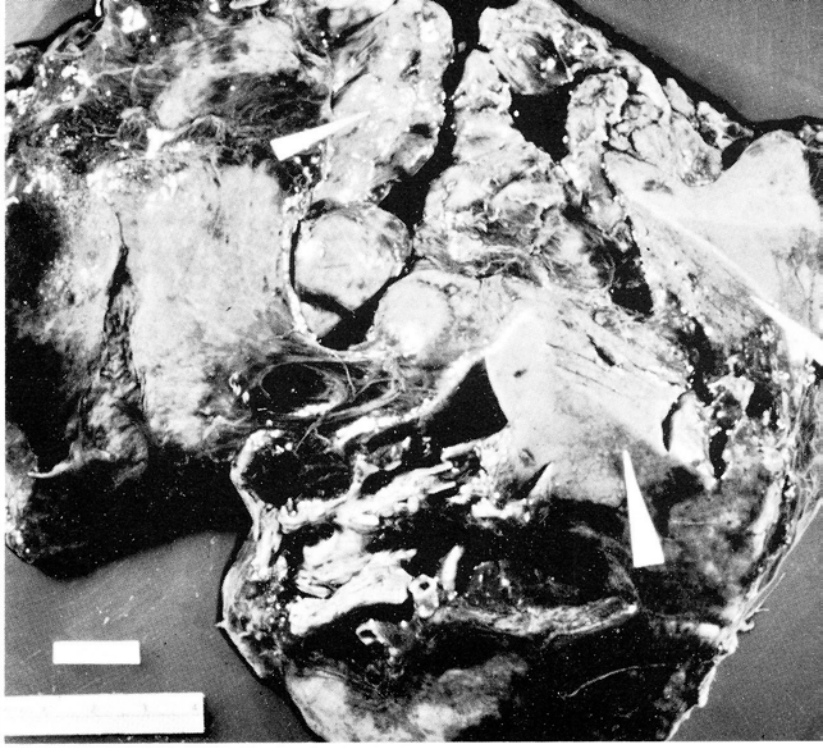


Fig. 1—Non-homogeneous density of the right lung obliterating the right heart border.

Fig. 2—Specimen of pulmonary lobectomy showing cross-section appearance of lesion.

Dr. Regato: Dr. E. Salzman, of Denver, also suggested middle lobe pneumonia due to bronchial obstruction; Dr. Neal Goodman, of Denver, offered pseudolymphoma; Dr. J. W. Travis, of Topeka, suspected a pulmonary "lymphoma". Drs. N. Kelly and N. Pliskin, of Philadelphia, offered lipoid pneumonia. Dr. Carlo Sirtori, of Milan, preferred lymphosarcoma.

Operative findings: On December 7th, 1965, a right middle and lower lobectomy were carried out. A firm tumor 5.5 x 4.0 x 3.5 cm was found in the medial segment of the middle lobe; another mass 7 x 5 x 2 cm in the medial basal segment of the lower lobe; a satellite hilar nodule 2.0 x 1.7 x 1.0 cm near the latter mass; and a fourth mass 6.0 x 7.0 x 4.5 cm in the posterior basal and lateral basal segments of the lower lobe. None of these masses seemed to arise from the bronchial tree.

Dr. Rappaport: The lesion consists of a fairly uniform cellular population. It is sharply demarcated against the uninvolved pulmonary parenchyma (Fig. 3). This line of demarcation might even be the limit of a lobe or of a pulmonary segment. The pleura is infiltrated by the cells of which this lesion is composed. Bronchi and bronchioli and cross sections of vascular connective tissue are evident within a heavy interstitial infiltration that has obscured the pulmonary parenchyma.

Higher magnification shows that the lesion is composed entirely of well differentiated lymphocytes. Mitoses were seen only after long search and it was not possible to determine whether these mitoses were in lymphocytes or in histiocytes, which were scattered among the predominating lymphocytes. Small clusters of histiocytes that contained anthracotic pigment were also evident throughout the lesion which apparently had not destroyed all pre-existing cellular elements. After search, occasional plasma cells were found; they were very scarce.

At very high magnification (Fig. 4) the uniformity and the mature appearance of the lymphocytes are particularly striking. If one were to see this type of cellular proliferation in a lymph node, the architecture of which has been completely obliterated, one would certainly consider the possibility of malignant lymphoma of the well differentiated lymphocytic type. In the lung, however, I could not come to the same conclusion, particularly in view of the experience of others who have shown that most, if not all, of these cases apparently do not behave as neoplasms. I might add that in my own experience the proliferation of mature appearing lymphocytes in extranodal locations does not have the same significance that it has in lymph nodes.

My first diagnosis was "tumor-like lymphocytic infiltrate of lung". This is equivalent to pseudolymphoma. Then I changed it to "lymphocytic tumor, probably benign" because I had some doubt whether I could really be unequivocal about the non-neoplastic nature of this lesion. After having lived with it for a while, I am now changing it back to my original diagnosis.

I believe that this is a so-called "pseudolymphoma". Since I do not like the term "pseudolymphoma", my final diagnosis in this case is "tumor-like lymphocytic infiltrate of lung".

Dr. Rappaport's diagnosis: TUMOR-LIKE LYMPHOCYTIC PULMONARY INFILTRATE, Probably Benign.

Histopathologic Diagnoses Submitted by Mail

Lymphosarcoma	32
Benign lymphocytic lymphoma	19
Malignant lymphoma	65
reticular 4	
blastic 4	
cytic 48	
Pseudolymphoma	28
*Hodgkin's disease	2
Eight others	22

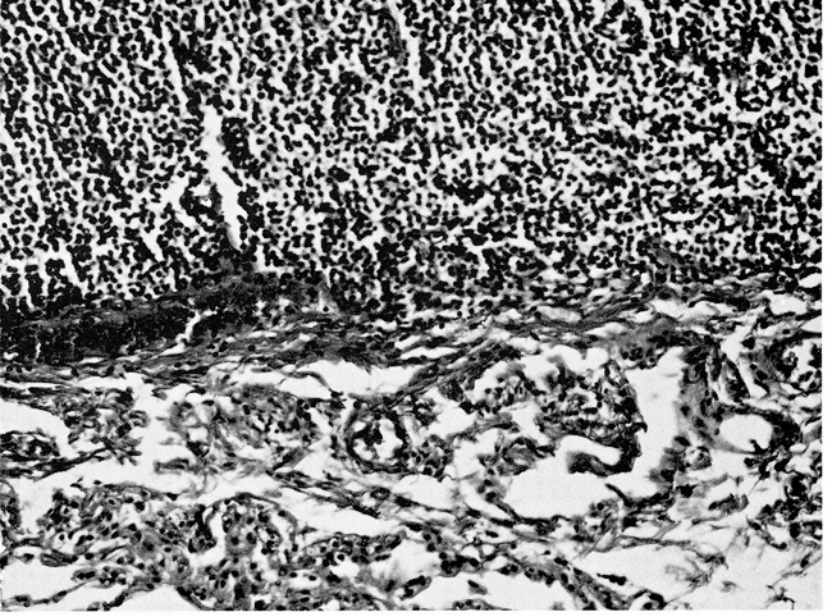


Fig. 3—A sharp line of demarcation separates the pulmonary lesion from uninvolved pulmonary parenchyma. (H & E x 250)

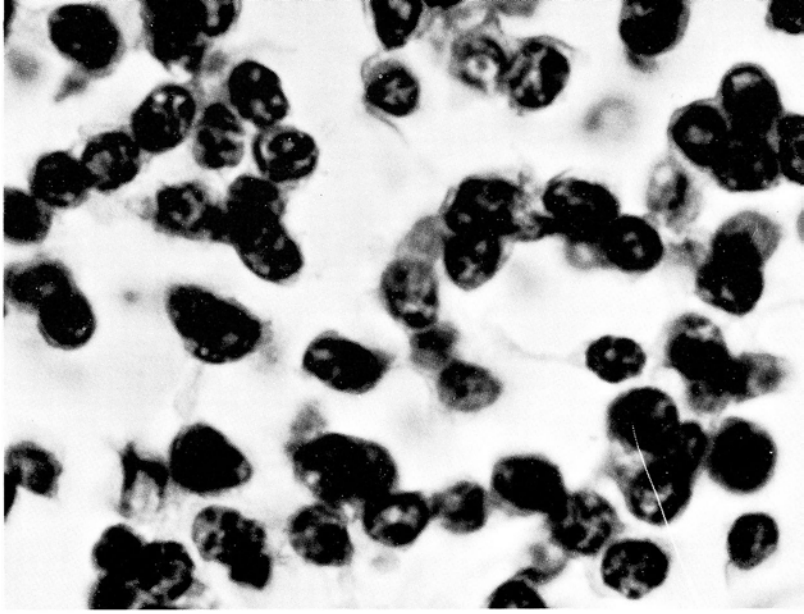


Fig. 4—The pulmonary lesion is entirely composed of mature appearing lymphocytes that show little variation in size, shape, or staining quality of their nuclei. Their cytoplasm is scant. (H & E x 1000)

Dr. Rappaport: The majority of the pathologists who saw this lesion called it a lymphosarcoma or malignant lymphoma. There is a minority who called it benign lymphocytic lymphoma or pseudolymphoma for a total of 47 adherents to this view which coincides with mine.

Dr. Regato: Dr. W. J. Frable, of Richmond, Virginia, also made a diagnosis of benign pulmonary lymphocytoma; Dr. M. R. Abell, of Ann Arbor, made a diagnosis of lymphocytic disease of the lung; Dr. Leo Lowbeer, of Tulsa, called it a reactive non-neoplastic pulmonary lymphoma; Dr. V. M. Arean, of Miami, Dr. R. L. Font, of Washington, D. C., and Dr. R. J. Lukes, of Los Angeles, designated it as a pseudolymphoma.

Alvin O. Severance, M. D., San Antonio, Texas: We thought of this as a lymphosarcoma; not having the experience that Dr. Rappaport had about extranodal behavior of these lesions. This patient is alive and well at this time, happily employed as a driver of a tractor; he was last seen six weeks ago. No radiotherapy or chemotherapy was used.

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7. Thymoma with Giant Cell Myocarditis

Contributed by MacCallum Reinhoff, M. D., Denver, Colorado

and W. C. Black, III, M. D., St. Louis, Missouri

THE PATIENT was a 14-year old boy in June, 1964, when he had to be put in a respirator because of severe dyspnea and cyanosis. On examination there was evidence of generalized muscular weakness but no wasting. Total proteins were 6.7 gm per 100 ml; uric acid 13.5 mgm %; SGOT 316 units and hematocrit 54%.

Dr. Mellins: The retrosternal space is filled by a large tumor which extends to the left and is not separated from the heart shadow. The left dome of the diaphragm is elevated and the trachea is displaced slightly to the right. The bones appear normal.

The anterior mediastinal tumors to be considered include teratoid tumor, lipoma, cystic hygroma, lymphoma and thymic tumors. Teratomas are round or oval and often contain calcifications. Lipomas are usually in the lower half of the thorax. Cystic hygromas are also usually seen in the lower half of the retrosternal region and are round or oval masses about 5 centimeters in diameter. Thymic malignancies, usually lymphosarcomas in children, are closely applied to the heart. They are locally invasive and may extend through the chest wall and diaphragm. They have been seen to lead to acute lymphatic leukemia in as short a time as six weeks. Some of the tumors are associated not with anemia but with polycythemia, which could produce the elevated hematocrit and elevated blood uric acid levels shown by the patient.

Dr. Mellins' impression: THYMIC LYMPHOSARCOMA (associated with leukemia?).

Roentgenologic Impressions Submitted by Mail

Thymoma	63
'Lymphoma'	25
Hodgkin's disease	18
Leukemia	12
Others	13

Dr. Mellins: I really do not know how to comment about lymphoma, in a general sense. The location along the left side of the heart, not involving hilar nodes, and in the anterior-superior mediastinum, would tend to speak against Hodgkin's disease. The diagnosis of leukemia has something to recommend it on laboratory grounds. The gross pathology is that of thymic tumor but I am worried about the laboratory data and suggest a lymphosarcoma with associated leukemia.

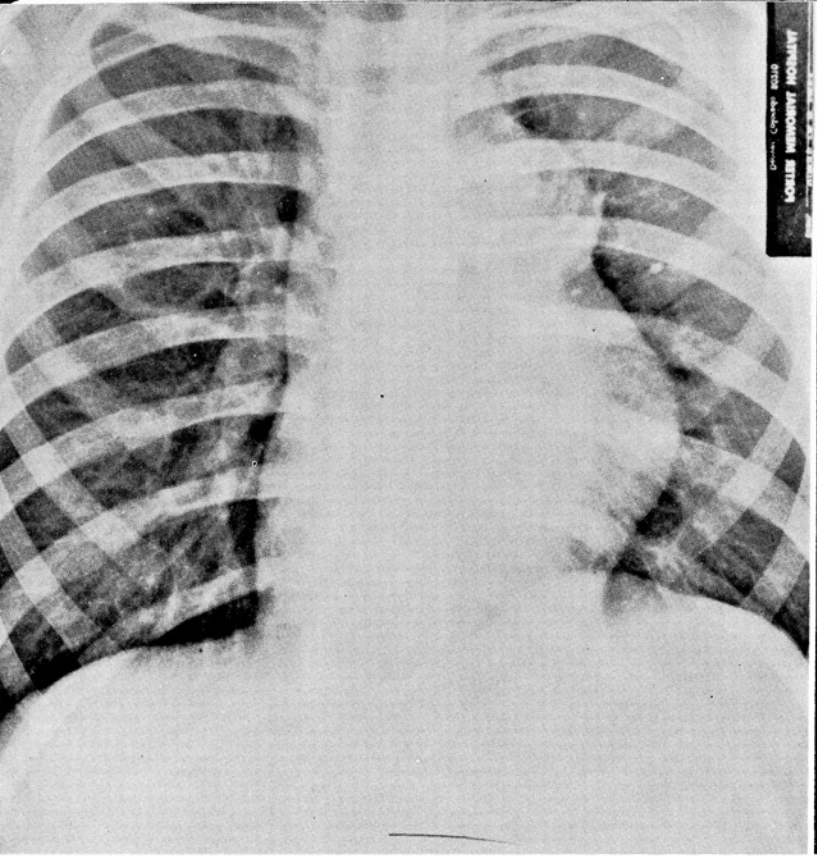


Fig. 1—Large tumor of the anterior mediastinum extending to the left side and displacing the trachea.

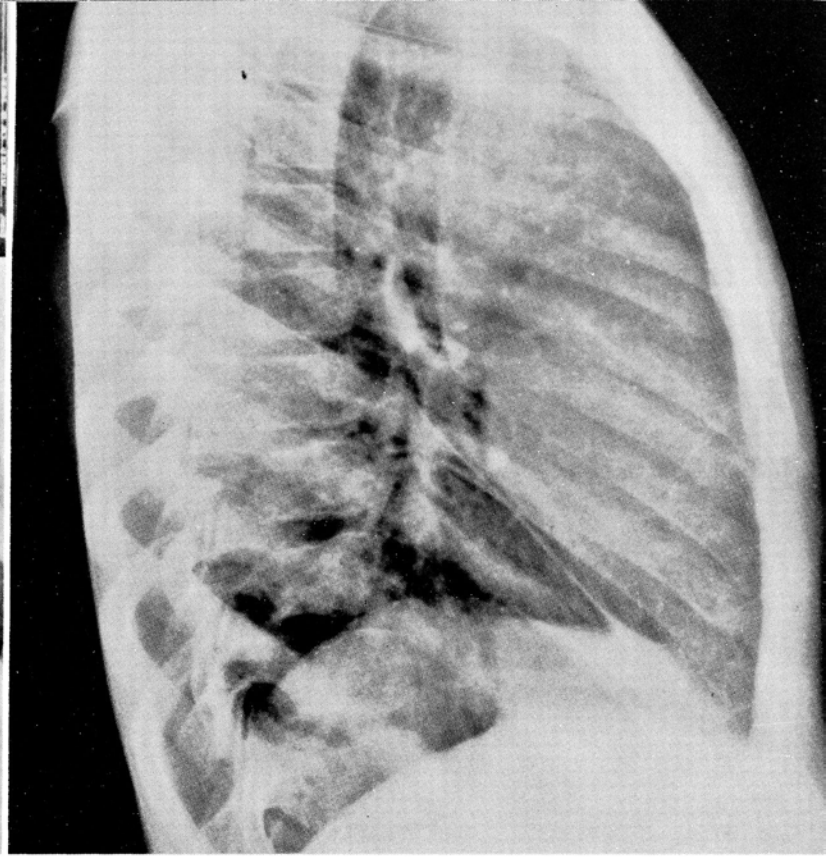


Fig. 2—Lateral roentgenogram shows anterior situation of tumor.

Dr. Regato: Dr. R. J. Kurth, of Lackland Air Force Base, Drs. H. Perlman and S. Lee, of Philadelphia, and Dr. J. Lemon, of Denver, suggested thymoma; Dr. B. Felson, of Cincinnati, made a diagnosis of malignant lymphoma arising in the thymus with secondary gout! Dr. R. Hill, of San Antonio, also made a diagnosis of lymphosarcoma.

Subsequent history: The patient was put on penicillin and prednisone; on the fourth day of admission he became more cyanotic and expired. The autopsy revealed the presence of a tumor of the anterior and posterior mediastinum, extending along the hilus of the left lung and infiltrating the lung itself. The myocardium appeared grossly infiltrated; there was no evidence of tumor outside the thoracic cage.

Dr. Rappaport: This tumor is characterized by cellular areas separated by broad branching strands of collagenous stroma (Fig. 4) that are evenly distributed throughout the tumor. The cellular areas have an epithelial component and a lymphocytic component (Fig. 5). This is characteristic of all primary thymomas, with the lymphocytic and epithelial components showing variable degrees of preponderance. The lymphocytes are small and mature-appearing. The epithelial component has some spindle-shaped cells. Most of the cells are clearly recognizable as epithelial elements, both in pattern and in cytology.

It is interesting that a histologically similar thymoma has been reported recently (Rosen), presenting with a pulmonary metastasis. As you know, thymomas can metastasize but do so very rarely. You did not receive in your Cancer Seminar slide box a slide of this patient's myocardium that showed a giant cell myocarditis such as had been reported in association with thymomas (Funkhouser; Langston; Waller).

Dr. R. Lattes has subdivided thymomas into the following types: 1) a predominantly lymphoid type, in which half of the patients have myasthenia; 2) a spindle-cell type, a small proportion of which are associated with aregenerative anemia; 3) an "epithelial" type; one-half of these have associated myasthenia and 4) a "rosette" or "pseudorosette type"; about one-third of these are said to be associated with myasthenia gravis. Dr. Lattes added two other "thymic tumors", the precise origin of which is controversial. One of them is the so-called "granulomatous thymoma". We interpret the lesion called granulomatous thymoma by Dr. Lattes as nodular sclerosing type of Hodgkin's disease. Some of the illustrations in his article resemble this form of Hodgkin's disease very closely. Dr. Lattes did consider Hodgkin's disease in the differential diagnosis and in his paper put "Hodgkin's disease" after the diagnosis of granulomatous thymoma, but for reasons that are given in his article he has come to the conclusion that these are, in fact, tumors of thymic origin. This is an area of difference of opinion between Dr. Lattes and other observers that has yet to be resolved. The sixth type of thymoma that is listed in Dr. Lattes' paper is the one which has seminoma-like features and which I prefer to regard as dysgerminoma of the anterior mediastinum.

Dr. Rappaport's diagnosis: THYMOMA.

Histopathologic Diagnoses Submitted by Mail

Thymoma		134
invasive	9	
spindle	8	
mixed	6	
epithelial	15	
malignant	26	
plain	70	
*Hodgkin's disease		2
Others		15

Dr. Rappaport: There has been a unique agreement on this case, except for the diagnosis of "malignant thymoma" made by 26 pathologists; I really do not know upon what criteria one can establish or rule out a malignant connotation. Perhaps one of those who made this interpretation might wish to comment on it.

Dr. Regato: With variations in garniture, the experts agreed on a diagnosis of thymoma in a patient with clinical signs of myasthenia gravis. Sections of the myocardium were originally submitted to Dr. B. Castleman, of Boston, who concluded that the changes were inflammatory, not neoplastic. Dr. R. Lattes, of New York, was of the same opinion, but was less definite. Dr. L. V. Ackerman, of St. Louis, also thought that the myocardium was not truly invaded.

Dr. Steinfeld: This was a critically ill boy with a large mediastinal mass and very likely myasthenia gravis; he had a very high uric acid which, in the presence of a normal BUN and in the absence of gout and of dehydration, reveals a significant turnover of large amounts of nuclear protein. A large mass such as this, compromising breathing and circulation, would represent, in our opinion, a chemotherapeutic emergency. Despite how critically ill this young man was, he probably should have received a single large dose of Nitrogen mustard along with supportive care. I notice corticosteroids were administered. Even though the tumor might not be significantly responsive to this form of therapy, it is conceivable that he would have had some shrinkage, allowing him to breathe a little more easily and perhaps ultimately become able to stand an operation. Prostigmine perhaps was given; this too could have resulted in some increase in strength and in his ability to exchange air and might have permitted him to survive a little longer and be operated. We have seen several patients with thymomas and pure red cell aplasia. But in patients with pure red cell aplasia the erythropoietin levels are very high; one of our two patients had calcifications in her thymoma.

Capt. Michael O'Brien, MC, Fort Carson, Colorado: There have been a number of articles about antinuclear and antimuscle antibodies in patients with thymoma; this patient had a giant cell myocarditis. I wondered if these antibody titers had been done or had been thought of.

Dr. Rappaport: One of the articles to which I previously referred had a report of both giant cell myocarditis and the LE phenomenon. This is an observation that has been made and recorded (Funkhouser).

Dr. Mellins: I would like to ask Dr. Steinfeld if he would clarify for me his interpretation of the uric acid.

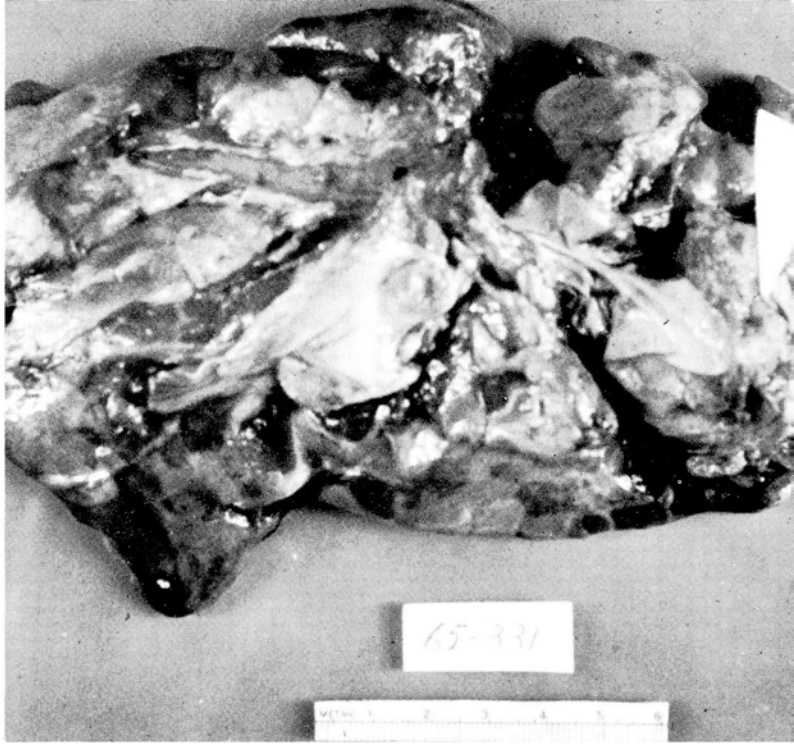


Fig. 3—Gross appearance of autopsy specimen of lung showing pleural implants.

Dr. Steinfeld: If the BUN were normal and the uric acid were very high as it is here in the absence of dehydration, I would presume then that this represented turnover of large numbers of cells. This could occur with polycythemia vera in acute lymphocytic leukemia and myeloid metaplasia and chronic granulocytic leukemia. However, if the BUN were quite high and he were dehydrated, I would have discarded the uric acid as having any meaning other than as a reflection of retention of all nitrogenous waste.

Matthew H. Block, M. D., Denver, Colorado: This is the one case where had the patient been operated upon, a smear or frozen section would have been useful; had he been found to have a lesion that was loaded with small lymphocytes, then he would have been a candidate for either immediate radiotherapy or immediate chemotherapy. On the other hand, if the lesion did not show that characteristic, then I do not think any type of therapy would have helped him very much. This type of lesion, such as

Fig. 4—Thymoma: Note the broad bands of collagenous tissue separating cellular areas that are composed of large cells with pale nuclei, and small cells with dark, round nuclei. (H & E x 35)

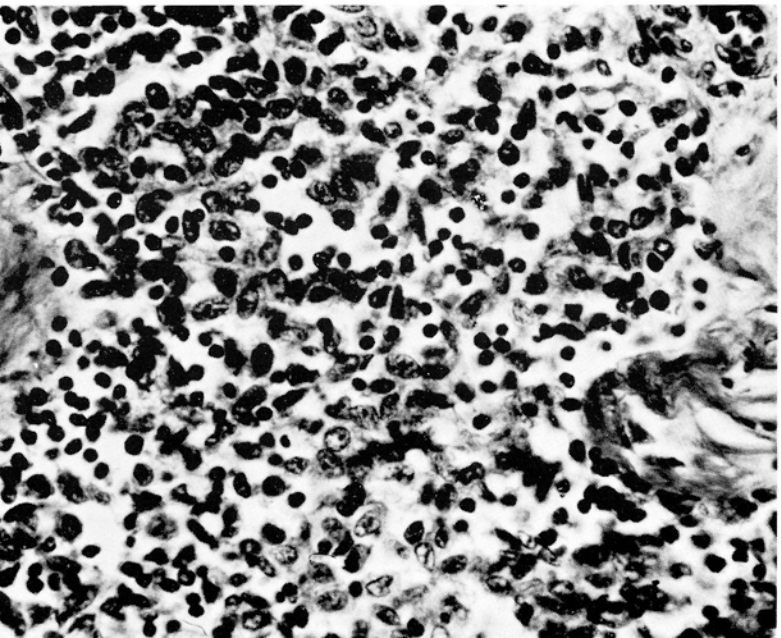
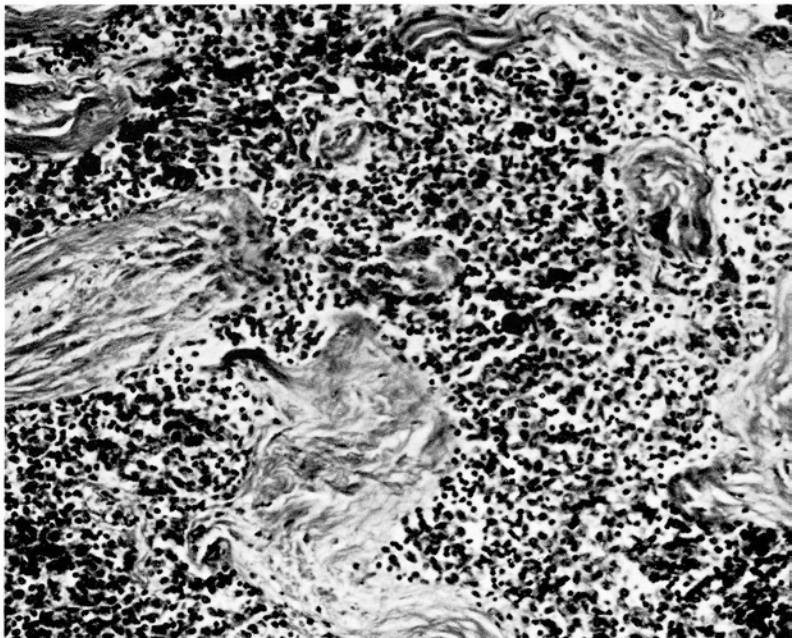


Fig. 5—Thymoma: at high magnification, note the mixture of epithelial cells and small mature appearing lymphocytes. (H & E x 250)



this patient has, with predominantly large cells, predominantly epithelial cells, does not really respond too well. I have had patients like this and I have managed to carry them along; in this case there were predominantly large cells and it was an obstructive lesion; the patient would have probably done better, temporarily at least, by an attempt to relieve the obstruction.

Dr. Rappaport: Histologically, the myocardium showed extremely severe inflammatory changes. This suggests that the myocarditis contributed at least as much to the patient's cardio-respiratory difficulties as the anterior mediastinal mass.

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8. *Vertebral Sclerosis, Cause Unknown*

Contributed by C. T. Kelso, M. D., C. W. Brown, M. D. and R. F. Berris, M. D.

Denver, Colorado

THE PATIENT was a 34-year old woman in April, 1964, when she gave a history of increasing pain in the interscapular region which had become constant, in spite of the administration of Demerol, and radiated to both arms. On examination there was tenderness to percussion of the upper dorsal spine, no splenomegaly and no adenopathy. Hemoglobin was 12.4 gm %; there were 6,000 WBC with 49% lymphocytes.

Dr. Mellins: The seventh thoracic vertebra is sclerotic but normal in shape. The ribs, scapulas and clavicles are normal. No paraspinal masses are seen.

Paget's disease can produce a solitary sclerotic vertebra but the patient's age and the absence of vertebral enlargement and trabecular coarsening are against this diagnosis. The patient's age and the uniform involvement of but a single vertebra speak against metastatic malignant tumor. Spinal canal tumors can produce single ivory vertebrae as can spindle cell sarcoma of the vertebra. Occasionally, as, I think, in this case, osteosclerosis is the initial manifestation of Hodgkin's disease. In these cases fever of unknown origin, particularly periodic fever of Pel-Ebstein type, is often present.

Dr. Mellins' impression: HODGKIN'S DISEASE PRODUCING OSTEOSCLEROSIS OF T7.

Roentgenologic Impressions Submitted by Mail

Hodgkin's disease	29
'Lymphoma'	20
Myeloma	13
God knows what!	1
Others	28

Dr. Mellins: Myeloma is an important thing to discuss. There are documented cases, truly in the minority, of plasmocytomas which are osteosclerotic. This has been reported occasionally since about 1951, to the best of my knowledge. Whereas I cannot exclude plasmocytoma, I would tend to speak against it because of the rarity of the plasmocytoma and lack of any other associated changes; I would be against the benign osteosclerosis because it is too uniform.

Dr. Regato: Dr. J. T. McClintock, of Denver, and Dr. B. H. S., of Ann Arbor, also made a diagnosis of Hodgkin's disease. Dr. E. Nava, of Ann Arbor, offered idiopathic vertebral sclerosis.

Operative findings: On May 6th, 1964, the body of the 7th dorsal vertebra was reached through a right sided thoracotomy, as much as possible was removed of the sclerotic bone and the defect filled with bone chips from the right ilium.

Dr. Rappaport: I was wondering what relation this case had to the special area of pathology in which I am interested. Since I did not expect that I would be given a case of Paget's disease, I completely discounted this possibility and I was more interested in the cellular composition of the marrow than in the bone changes, although it is very evident that the bone shows trabecular hypertrophy and, as you will see later, an increased degree of osteoblastic activity. The bone marrow is hyperplastic (Fig. 2); there are more cells and there is less fat than one ordinarily sees. When a hematologically oriented pathologist sees the hypercellular marrow associated with osteosclerosis, he will do a reticulin stain to see whether there is, perhaps, early myelosclerosis, which is manifested by an increase in the amount and density of reticulin fibers; this was done with negative results. Thus, the bone marrow showed nothing more than non-specific hyperplasia.

As far as the bone is concerned, the only feature that is conspicuous in addition to the trabecular hypertrophy is the presence of rows of osteoblasts along many of the osseous trabeculae. The result of this increased osteoblastic activity is readily apparent: it is manifested by a sclerosis of bone which remains otherwise unexplained.

In summary, I really do not have the faintest idea what hematologic disorder underlies this particular localized sclerosis of bone and I made the diagnosis: "sclerosis of bone, type and cause not apparent from the sections available for study". I turned to our orthopedic surgeon for advice. He loaned me a roentgenogram which shows a localized sclerosis of bone; the sclerosis was localized in a thoracic vertebra, and the orthopedic surgeon told me that it was a case of mast cell disease. It is true that mast cell disease can produce sclerosis of bone, but it does so usually in children with urticaria pigmentosa, a cutaneous form of mast cell disease. I have not heard of any such case in an adult unassociated with some other manifestations suggestive of systemic mast cell disease such as has been reported by Dr. Braunstein, and by Efrati and associates. Since it would have been unusual for this to be mast cell disease, I looked at additional films and I saw that, in addition to the sclerotic lesion, there was an osteolytic lesion in another vertebra, which is a lumbar vertebra. In reviewing the histologic sections from the bone biopsy you can see an abnormal proliferation of cells in the marrow spaces. There is no normal or hyperplastic marrow left. These were the cells that were interpreted as mast cells. However, mast cell granules had never been demonstrated in these cells and the quality of these sections was really not good enough

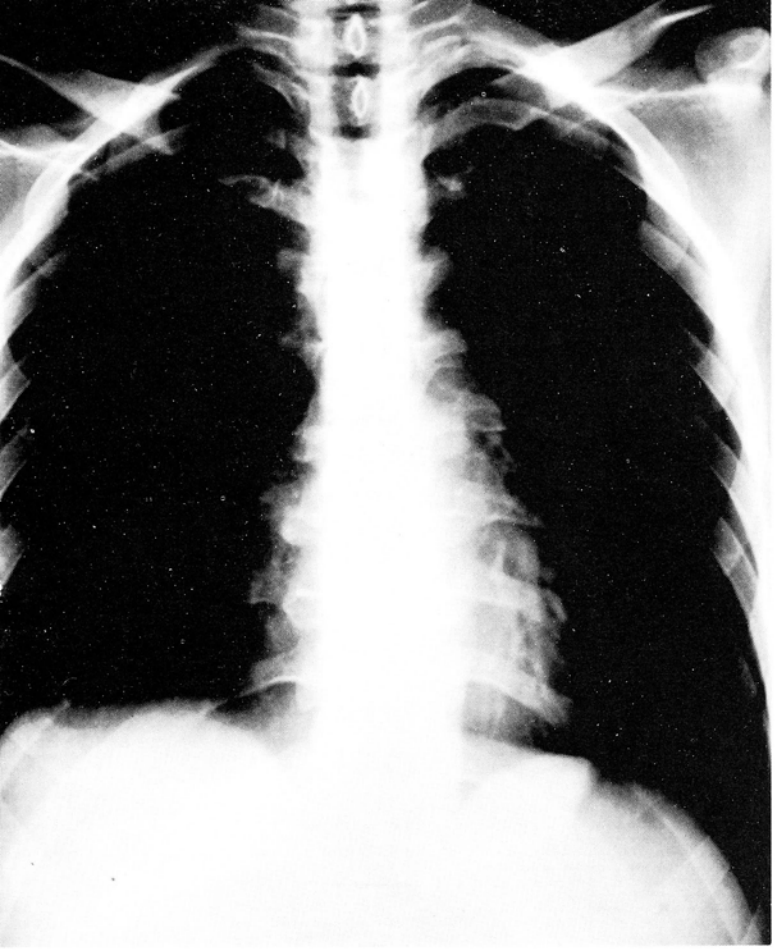
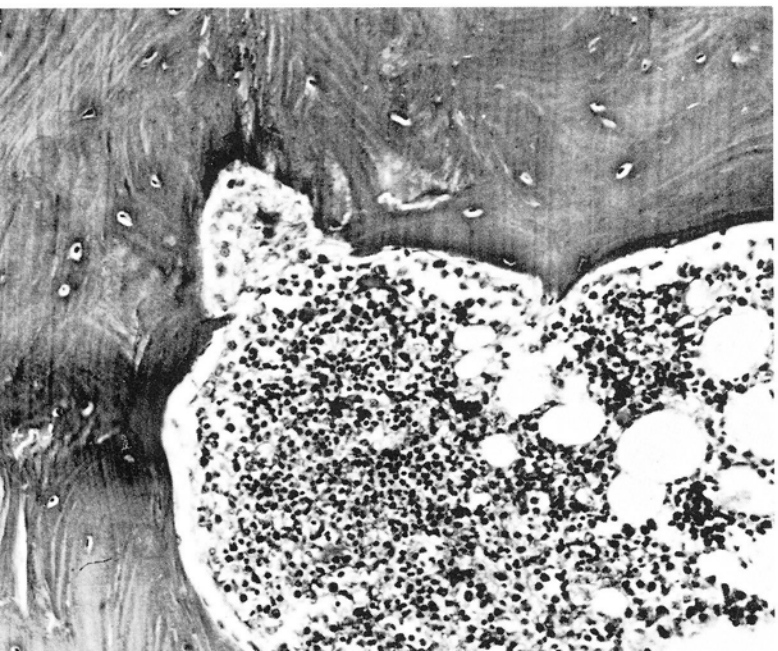


Fig. 1—Poor reproduction of a roentgenogram which shows sclerosis but normal shape of the seventh thoracic vertebra.

to decide what these cells were. However, in subsequent biopsies and at autopsy, this patient did have the classical microscopic findings of multiple myeloma and this apparently was one of the rare cases in which multiple myeloma showed both sclerotic and osteolytic lesions (Engels et al). When I made further inquiries, Dr. Peter Lazarovits, member of our department of radiology told me: "I know exactly what this patient has, Hodgkin's disease"; he showed me a film from a similar sclerotic lesion (Fig. 3); it was from a proven case of Hodgkin's disease. He reminded me that this picture was very typical of Hodgkin's disease involving a vertebra.

Fig. 2—The bone marrow is hyperplastic. The bony trabeculae are thickened and lined with rows of osteoblasts. (H & E x 100)



Dr. Rappaport's diagnosis: SCLEROSIS OF BONE and BONE MARROW HYPERPLASIA.

Histopathologic Diagnoses Submitted by Mail

Osteosclerosis	37
Eosinophilic granuloma	30
Marrow hyperplasia	24
*Hodgkin's disease	29
Paget's disease	10
Eleven others	37

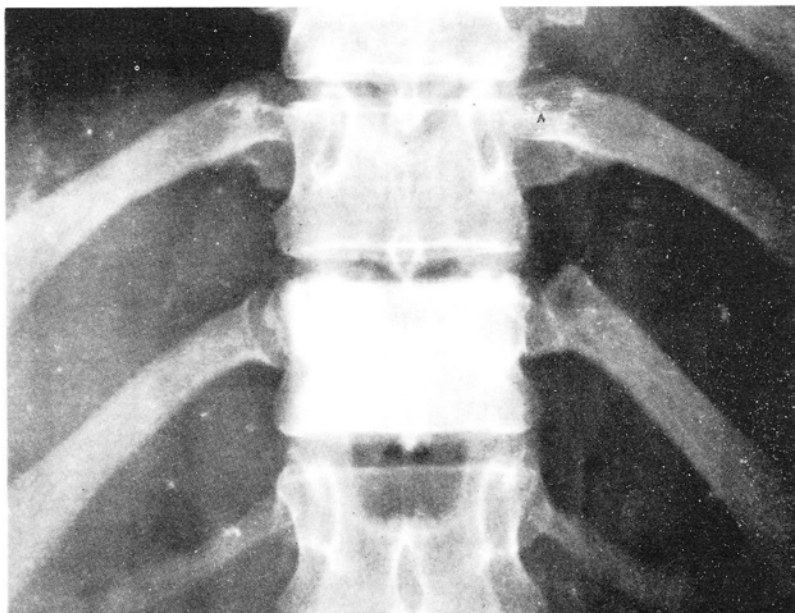
Dr. Rappaport: With the possible exception of marrow hyperplasia, I really cannot agree with any of the diagnoses made here; even marrow hyperplasia does not account for the bone changes. I do not know upon which histologic feature the diagnosis of Hodgkin's disease was based; perhaps this diagnosis was made because of the characteristic radiologic findings: I saw nothing in the sections to substantiate this diagnosis. As to the diagnosis of eosinophilic granuloma, there is really no evidence for it. I do not believe that we need consider Paget's disease because it would not have been chosen for this Cancer Seminar. As to osteosclerosis, I do not believe that one is justified in using this term for an isolated sclerosis of bone. Osteosclerosis is usually and historically considered a systemic disorder as indicated by the term "osteosclerotic anemia" which is an old term for the entity of myelosclerosis with myeloid metaplasia that is associated with osteosclerosis. Another hematologic disease that may be associated with osteosclerosis is chronic granulocytic leukemia. This is a rare occurrence, much rarer than the osteosclerosis that is observed in myelosclerosis with myeloid metaplasia, so-called "agnogenic myeloid metaplasia".

In summary, I would call this "vertebral sclerosis, etiology undetermined". Similar lesions have been reported under the designation of idiopathic vertebral sclerosis (Ackermann and Schwarz). I do not believe that the patient has either a malignant lymphoma or a leukemia or any other primary disorder of the hematopoietic system.

Dr. Regato: Dr. J. Kissane, of St. Louis, and Dr. V. M. Areán, of Miami, made also a diagnosis of osteosclerosis. Dr. W. R. Platt, of St. Louis, offered a diagnosis of myelo-proliferative disease or non-lipid histiocytosis, but admitted that he needed more dope! Dr. R. H. Stienmier, of Denver, and Dr. B. Peison, of Chicago, submitted Hodgkin's disease.

Subsequent history: The pain was relieved following operation but it recurred; a right pleural effusion failed to reveal malignant cells. The patient developed a case of anxiety and was put in the hands of a psychiatrist. In September, 1964, she moved to California and was lost to view.

Fig. 3—Roentgenogram showing localized sclerosis of the eleventh thoracic vertebra in another patient with known Hodgkin's disease.



Dr. Steinfeld: I do not know what she had either. She developed a right pleural effusion but that apparently may have been related to the thoracotomy. Otherwise, one would have to think she had more than this single lesion in the vertebra. If this patient had myeloid metaplasia involving other bones, even though it might not be visible radiographically, her blood smear should show an isocytosis and poikilocytosis, a polychromasia of her red cells, bizarre platelets, and a reticulum-cell count which would be a little high because she is releasing young red cells. Also, bone marrow sections from other parts of her body would be useful, if we were going to try to find out what was going on in this lady, assuming that her disease is not necessarily localized. The alkaline phosphatase may be very high in myeloid metaplasia; it also may be very low, or may be normal. The uric acid level might be high in a patient with myeloid metaplasia. Also, the acid phosphatase might be high in this condition. With localized disease and severe pain requiring narcotics and visits to a psychiatrist, it would be worth considering the use of radiation therapy.

Dr. Regato: We realize that you use radiotherapy for psychotherapy sometimes, but that is not an indication in our view.

Weldon K. Bullock, M. D., Los Angeles, California: I would like to ask Dr. Rappaport if he has had the opposite occur where you have a large lytic lesion of bone without fibrosis, with similar findings.

Dr. Rappaport: I have seen lytic lesions in which we simply could not account for the radiologically demonstrated osseous rarefactions on the basis of histologic study of curretted material. There was no fibrosis; histologic sections of the curretted tissue showed either hyperplastic or normal bone marrow, and atrophy as well as scarcity of bony trabeculae. I have only seen two such cases and was not able to offer a diagnosis in either. Neither of them were suggestive of any primary disorder of the hematopoietic system. They were bone diseases of a peculiar nature that I could not diagnose.

C. T. Kelso, M. D., Denver, Colorado: Several pathologists saw this initially and a few of them considered Hodgkin's but noboby could go as far as to make that diagnosis; it was signed out as a focal osteosclerosis and marrow hyperplasia. The patient did fairly well for the next six or eight months before she moved away.

Dr. Regato: It was two years and three months ago that she was lost to view. What do you figure has happened to the patient by now? What is your prognosis?

Dr. Kelso: We did not make a diagnosis of any bad disease.

Dr. Regato: I have news for you. I talked to the patient on the telephone day before yesterday, and also to her physician. She is not in California; she is in Kansas; she has an occasional pain in the back that is relieved by antispasmodics and has no other trouble except psychoneurosis.

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9. Histiocytosis of the Eyelid

Contributed by T. N. Vincent, M. D. and R. Miercort, M. D.

Denver, Colorado

THE PATIENT was a 20-year old woman in July, 1965, when she complained of fatigability, fever and 30 pounds weight loss. There was swelling of the left lower eyelid, large nasal polyps and voluminous bilateral upper cervical and submaxillary lymphadenopathy, larger on the left side; there was no splenomegaly. The hemoglobin was 11.5 gm %; WBC normal; sedimentation rate 53 mm/hr; total proteins 7.9 gm %.

Dr. Mellins: Ilio-pelvic and aortic lymphadenography reveals mild enlargement of the component lymph nodes. Many show breaks in the outline of the marginal sinus. The lung fields appear clear except for the presence of contrast-filled lymph nodes in the medial portion of the left supra clavicular space. A short band-like structure probably represents the termination of the thoracic duct.

Initial hopes that lymphography would be made to yield reliable gross pathological information have not yet materialized. The nature of the contrast media used and the presence of unimportant anatomic changes in lymph nodes result in deceptive radiographic appearances. Some appearances seem to occur with reasonable frequency and may suggest the diagnosis with modest accuracy.

Enlargement of nodes occurs in malignant disease of all kinds, but interruption of the marginal sinus favors a diagnosis of metastatic carcinoma or reticulum cell sarcoma. In the former the boundary between normal tissue and the metastasis tends to be blurred. Hodgkin's disease and chronic lymphatic leukemia tend to produce a bead-like pattern of contrast distribution and the margin sinus remains intact.

Dr. Mellins' impression: RETICULUM-CELL SARCOMA.

Roentgenologic Impressions Submitted by Mail

"Lymphoma"	28
Hodgkin's disease	25
Reticulum-cell sarcoma	9
Lymphosarcoma	8
Sarcoidosis	8
Others	38

Dr. Mellins: Chronic lymphatic leukemia and Hodgkin's disease have intact marginal sinuses. I must say I have not seen very much in the way of lymphangiography in sarcoidosis. One might expect that one would see enlargement of the node and chronic inflammatory response but I have not seen enough abdominal lymphangiography in sarcoidosis to have an opinion.

Dr. Regato: Dr. E. Salzman, of Denver, submitted an impression of polyclonal gammopathy! Dr. N. W. Courtney, of Ann Arbor, preferred reticulum-cell sarcoma. Dr. N. Kelly, of Philadelphia, offered Hodgkin's.

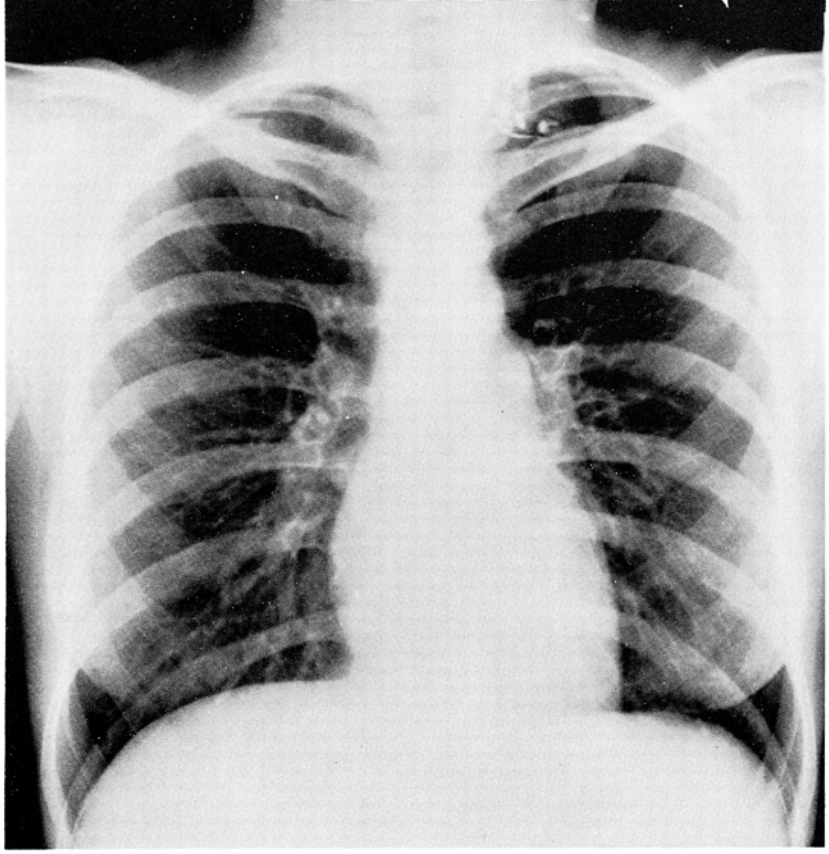

Fig. 1—Lung fields appear clear and there is no abnormality except for the presence of contrast material in lymph nodes of left supraclavicular region.

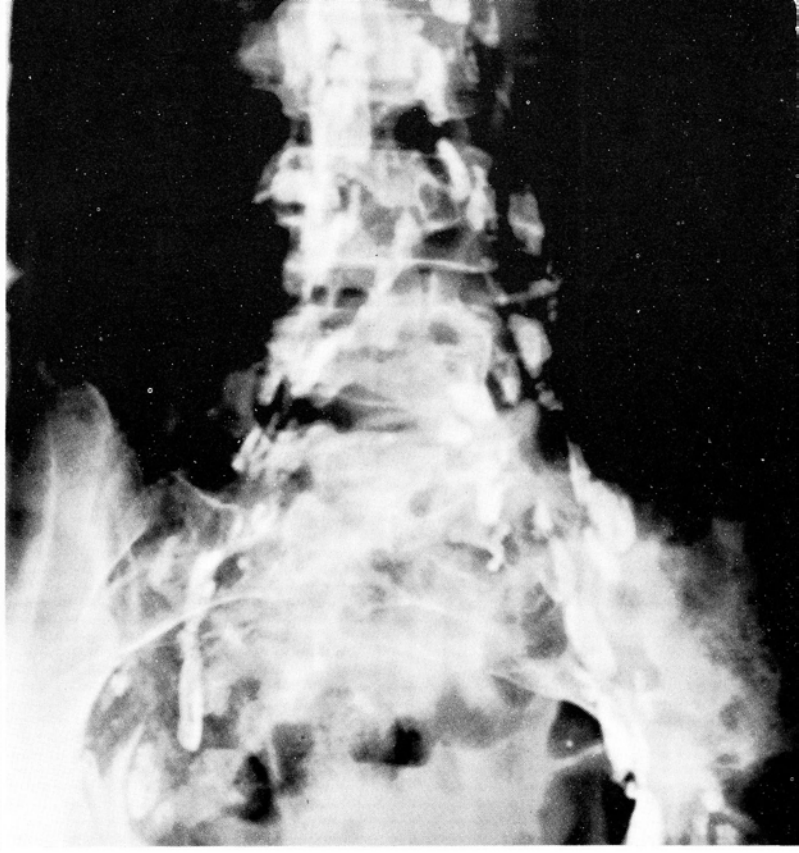

Fig. 2—Lymphadenography shows mild enlargement of lymph nodes, many of which show breaks in the outline of the marginal sinuses.

Dr. Rappaport: In this section of the lymph node you can clearly see three zones: a thick capsule (Fig. 3) which is moderately infiltrated with cellular elements; a narrow zone of well preserved tissue; and a zone showing the tissue to be altered by an artifact of fixation. It appears that the fixative had penetrated only up to and including the second zone. Either the lymph node was cut too thick at the time of the gross examination or it was placed into the fixative *in toto;* this is something I must caution you against. I will show you the excellent preservation of cellular detail in the subcapsular area and its poor preservation in the deeper area. Your sections show primarily the artifactually altered areas. You see widely dilated spaces filled with cells that I shall show you at higher power in a moment, and you see the compressed medullary cords containing remnants of lymphatic tissue. At higher magnification (Fig. 4) one can see large cells that have a very abundant amount of pale-stained cytoplasm which contains nuclear debris or intact nuclei; this indicates that we are dealing with a predominantly histiocytic proliferation that appears to be largely within sinuses. In addition, lymphocytes and plasma cells, including binucleated forms, are fairly abundant. Some of the plasma cells have Russell bodies. Focal areas of necrosis with many polymorphonuclear leukocytes and plasma cells are also evident.

Some of the numerous histiocytes look so disturbing that their possible neoplastic nature could be suspected. However, it is very difficult to evaluate cytologic features of cells that have not been promptly fixed, because any delay in fixation has a tendency to increase nuclear clumping and to make cells that initially have features of non-neoplastic cells resemble neoplastic cells. That is why it is so important to pay attention to the proper processing of lymph nodes, particularly to their prompt and adequate fixation. In the peripheral well fixed areas you see that the histiocytes look much better; they look like foam cells and they show the same intermingling with plasma cells and lymphocytes, as seen elsewhere.

The difficulty of diagnosing this case was further enhanced when one of my associates found a bi-nucleated cell resembling a Sternberg-Reed cell. I finally decided that in spite of the presence of this peculiar cell, the histologic picture did not appear to be consistent with Hodgkin's disease. I thought that this was a primarily histiocytic proliferation, a histiocytosis, in which most of the cells were devoid of cytologic features of neoplastic cells. However, there were some that looked disturbing. The differential diagnosis was between a differentiated progressive histiocytosis of the Hand-Schüller-Christian type and a malignant histiocytosis, and I could not make the decision on the basis of the available evidence. I, therefore, made a diagnosis, unsatisfactory as it may seem, of "histiocytosis, unclassified".

Dr. Rappaport's diagnosis: HISTIOCYTOSIS, unclassified.

Histopathological Diagnoses Submitted by Mail

Histiocytosis	52
*Hodgkin's disease	38
Plasmocytoma	12
Chronic lymphadenitis	29
Histiocytosis X-Y-Z!	1
Twelve others	28

Dr. Rappaport: The diagnosis of histiocytosis was made my most, and even though they did not say "unclassified", fifty-two of the participants did not commit themselves as to the type of histiocytosis. I can sympathize with them; I did the same thing. Thirty-eight made a diagnosis of Hodgkin's disease. This is understandable because of the occasional findings of binucleated histiocytic cells that resembled Sternberg-Reed cells. I did consider this diagnosis; however, since I could not find completely acceptable Sternberg-Reed cells and since the entire histologic picture did not fit Hodgkin's disease, I dismissed this possibility for serious consideration. I would not consider plasmocytoma because there is no evidence that the plasma cells are neoplastic.

Dr. Regato: Dr. J. Bauer, of St. Louis, made a diagnosis of malignant histiocytosis; Dr. J. Kissane, of St. Louis,

Fig. 3—The capsule of the lymph node is thickened. The peripheral sinuses are almost completely obliterated. The lighter areas represent aggregates of histiocytes with abundant cytoplasm. The darker areas represent collections of lymphocytes and plasma cells. (H & E x 25)

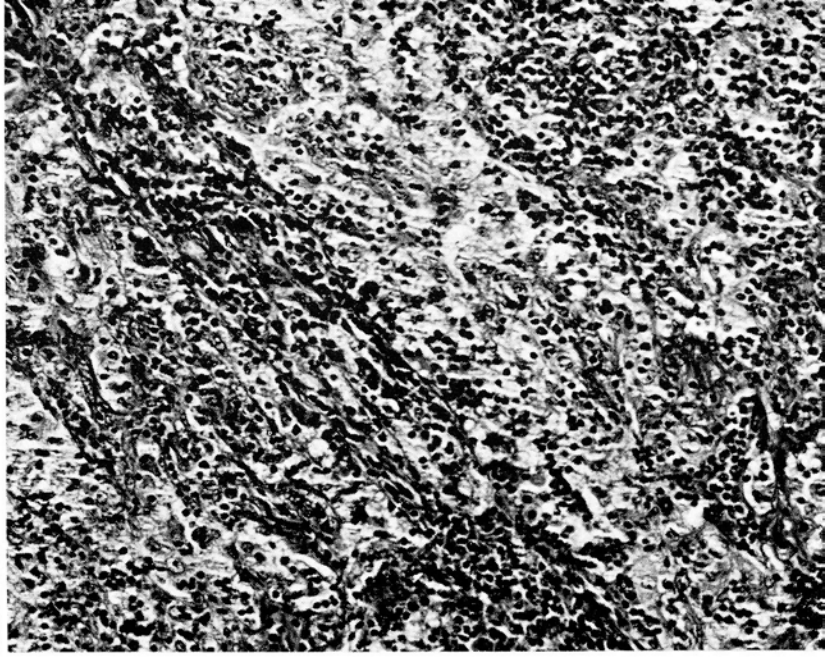

Fig. 4—Masses of histiocytes are evident in the sinuses and have infiltrated the medullary cords. (H & E x 100)

preferred sinus histiocytosis; Dr. M. R. Abell, of Ann Arbor, considered a reticulohistiocytosis and questioned the possibility of an adult Gaucher's. Dr. W. R. Platt, of St. Louis, called it a lipid histiocytosis; Dr. R. L. Font, of Pittsburgh, suggested a rare type of histiocytosis. Dr. H. A. Oberman and Dr. R. Nishiyama, of Ann Arbor, considered reactive lymph node hyperplasia due to phagocytized lipid. Dr. Asa Barnes, of Washington, D. C., made a diagnosis of Hodgkin's and pointed also at the artifacts of lymphangiography.

Subsequent history: On a histologic diagnosis of chronic granuloma of the eyelid and subacute inflammation of the nasal mucosa with reactive hyperplasia of cervical lymph nodes, the patient was discharged and put on 250 mg of tetracycline. In September, 1965, the patient was readmitted; there had been some occasional fever but no loss of weight; the cervical adenopathy was larger and tender; there was no splenomegaly. Liver function tests were normal; all skin tests were negative; the bone marrow biopsy was reported normal. The sedimentation rate was 49 mm/hr; the WBC were 20,600 per mm^3. Another bone marrow biopsy showed mild plasmocytosis. The patient was seen by Dr. Matthew Block who re-examined the histopathologic evidence: he found numerous reticulum cells but no Reed cells; he concluded that this was probably a "lymphoma" or an unusual storage disease. The slides were submitted to Dr. H. Rappaport who reported: "marked proliferation of relatively well differentiated histiocytes with abundant cytoplasm. The moderate nuclear variations and atypia are disturbing but not sufficiently pronounced to justify a diagnosis of malignant histiocytosis. I, therefore, would tentatively interpret this lesion as differentiated progressive histiocytosis of the Hand-Schüller-Christian type."

The patient was put on steroids: the fever disappeared, the white cell count dropped and there was some diminution of the cervical adenopathy. From October 11th to December 11th, 1965, the patient received radiotherapy to two lateral cervical fields, 12 x 10 cm, and a total of 4,900 R in 61 days; she also received 4,380 R directed to the nasal fossa.

In February, 1966, the patient complained of cough, fever, and sternal pain radiating to the right shoulder; there was some mediastinal widening and numerous small, hard, non-tender nodes in the neck, axillae and inguinal regions. She was last seen in June, 1966, when she was put on amethopterin; there were no bone lesions found.

Matthew H. Block, M. D., Denver, Colorado: One meets one's patients in the most unusual locations. I was looking at these slides and did not know who the patient was. I think we ought to realize that there are a couple of things about this lady that do not appear in the transcript. In the first place, this lady lost a tremendous amount of weight and she was quite emaciated. Like Dr. Rappaport, I looked at the biopsies and oscillated between a malignant lymphoma and Letterer-Siwe's disease; I guess I changed my mind about two or three times.

Dr. Rappaport: I do not remember this case. When I prepared the discussion for this Seminar, I had no recollection that I had seen the slides of either of the two cases on which I have been quoted as having given an opinion previously.

Dr. Regato: This is correct. I talked to Dr. Rappaport on the telephone day before yesterday, and already at that late date I said: "I hope you are aware that you have seen two of these cases before"; there was a long silence at the other end of the telephone, and I said: "Well, do not worry; right or wrong, you made the same diagnoses the other time".

Dr. Block: It is not any wonder you did not recognize the material because the slide that we sent was from lymph node material. The patient did become quite ill and for a while we thought that she would literally choke to death because of these huge masses in her neck and in her nasopharynx; that is when she received radiotherapy. We have adopted the attitude that if this lady eventually develops diabetes insipidus and holes in her skull, or an eosinophilic granuloma, then we will have to say in retrospect that this was the Leterer-Siwe variety of disease. If, on the other hand, as seems to be the case, she has a highly malignant course and develops an acute lymphatic leukemia, we will then have to conclude that our initial impression was wrong and that she really belongs in the malignant lymphoma group.

Dr. Steinfeld: We do not know exactly what we are treating, but the patient is very ill and, therefore, we must treat her. There is some argument certainly about the

treatment of Hodgkin's disease with steroids. There is a recent report by Tom Hall that steroids in larger than the conventional dosage, using about 120 mg a day, is helpful in Hodgkin's disease. One could ask: what is the malignant cell in Hodgkin's disease? Is it the Reed-Sternberg cell? the eosinophil? the fibroblast? the reticulum cell? or the lymphocyte? It is conceivable that the steroids with their lymphocytolytic effect would cause shrinkage of tumor and make the physician feel good but would really have no ultimate effect on the course of the disease. If there is a question of Hodgkin's disease and we are going to initiate therapeutic trials, it might be useful to use a drug in a fairly large dosage, and this would be Vinblastine. If fever disappeared and nodes shrank dramatically, this would be some evidence in favor of lymphoma, particularly Hodgkin's disease, and away from a lipidosis or reticuloendotheliosis. I am not really aware of many good results using Methotrexate for this group of diseases. However, when the disease becomes lymphoblastic, that is when a lymphoma is lymphoblastic, either in a child or an adult, Methotrexate is useful in proportion as it is useful in acute lymphoblastic leukemia. There are two other agents that are useful in reticulum-cell disease or blastic disease of this type. We do not like to use Vincristine because of the very serious neurologic disturbance associated with its continued use, although one can obtain a remission in childhood acute leukemia with three injections and thereby obtain a remission and not cause a neurologic disorder. But of all the alkylating agents, only one is useful in acute leukemia and that is Cyclophosphamide. In a recent randomized double blind study, Cyclophosphamide turned out to be more useful than Vincristine in reticulum-cell sarcoma.

I do not know what this lady has but what I would do would be to continue to biopsy nodes as they appear, in the hope that one of these would have a characteristic pattern that at least two pathologists would agree on and then I would proceed from there.

Ronald Dorfman, M. D., St. Louis, Missouri: With a certain amount of humility, because I really do not know what the cause of the disease is, I think this is the sixth patient with a pattern in the lymph nodes like this that I have seen over the last five or six years.

The first two cases were in Africa; one was a Negro child who had extremely enlarged cervical lymph nodes but, apart from this, was clinically very well; histologically the sinuses were dilated and filled with the identical histiocytes with large numbers of plasma cells and polymorphs. This boy had hypo-Gamma globulinemia as the only other abnormal finding. I would like to draw your attention to a recent paper (Azoury) describing an unusual case of histiocytosis, a young boy with enlarged lymph nodes with the identical pattern with histiocytic involvement of the testes, and with hypo-Gamma globulinemia. We have been reviewing the cases in our files that were diagnosed as malignant reticuloendotheliosis, and we have come across two more with this pattern. One is a child who fourteen years later is well.

Leo Lowbeer, M. D., Tulsa, Oklahoma: We had a case of a 10-year old child who developed very large lymph nodes in the right cervical region which were biopsied. Dr. Stout and Dr. Lattes called it a reactive histiocytosis. Dr. Rappaport called it a malignant reticuloendotheliosis. Dr. Gall was on the fence. The child developed lymph nodes in the mediastinum which spontaneously disappeared. Cortisone was administered; he is still on a minimum dose of Cortisone and seems to be extremely well. All the lymph nodes have disappeared. The only interesting feature in this particular child was that this developed after a smallpox vaccination before she went to Germany.

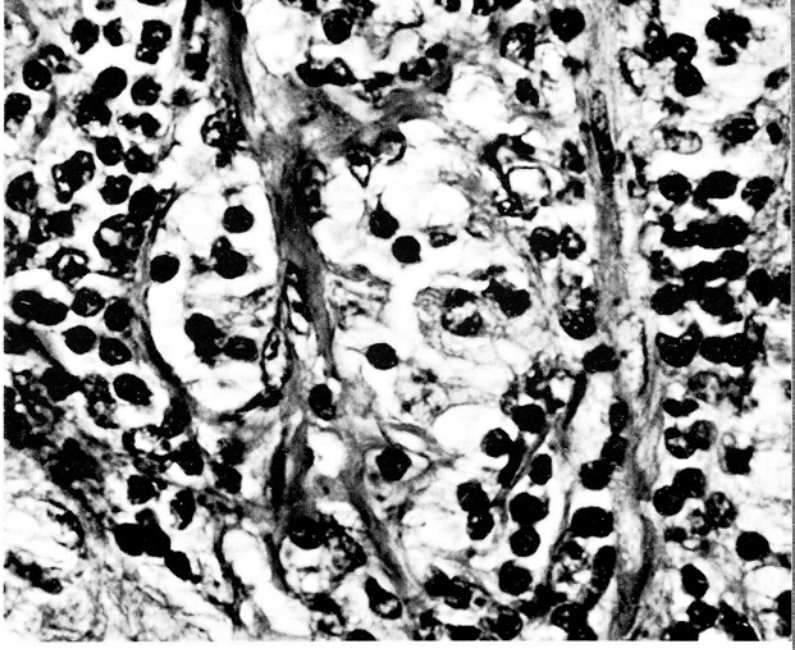

Fig. 5—At high magnification the histiocytes have abundant vacuolated cytoplasm. The histiocytic proliferation lacks distinctive features that would permit one to identify the precise nature of the patient's disease.

Dr. Rappaport: I was afraid that in the presence of so many pathologists some of my diagnostic errors would finally catch up with me and this is what just happened. I believe, however, that correctly diagnosed malignant histiocytosis is a rapidly progressive disease with a life expectancy of approximately six months to one year. I would say that a one and one-half year survival would be unusual and if the patient lives much longer the diagnosis of malignant histiocytosis is not tenable. I am very much concerned with the observation that early in malignant histiocytosis the proliferating histiocytes may look deceptively benign. Whether the present case falls into this category, I am unable to tell. So I still believe histiocytosis, unclassified, is the correct term for this histologic picture, even though it indicates our ignorance as to what specific disease this patient has. We should not force ourselves to make a diagnosis that would fit into an established clinical pattern, because new diseases and new syndromes are being discovered and described all the time. Dr. Dorfman's comments on this point are quite pertinent. I would say again that the length of survival in this case would militate against malignant histiocytosis.

Dr. Regato: Dr. Rappaport, do you think the lipid phagocytosis which was pointed out by some of the participants, due possibly to the lymphangiogram, is of any significance?

Dr. Rappaport: I did not know that the patient had a lymphangiogram. This, however, is not the histologic picture that has been described in lymph nodes of patients who have had lymphangiograms, nor would we expect to see changes attributable to this diagnostic procedure in a cervical lymph node.

Dr. Block: The biopsy was done before the lymphangiogram.

Dr. Steinfeld: If you see a patient every day in the hospital and the patient is losing weight, and febrile, and the family is asking what you are going to do, you can temporize just so long and ultimately come to a therapeutic trial.

Dr. Rappaport: May I make a comment, Dr. Steinfeld? Previously, in the course of these proceedings, you mentioned that you are treating these patients to toxicity; in other words, with doses high enough to produce marrow depression just short of complete aplasia. Do you not believe that this type of therapy might adversely affect the patient's immunologic resistance to his disease?

Dr. Steinfeld: Where we do not know what the disease is we must be very, very gentle with our therapy. The unfortunate thing with chemotherapy is that when the patient does not respond you do not know if it is because the disease is not responsive or you have not given enough drugs. The patient who does not respond is always taken to toxicity whereas some of the ones who do are not. In a situation such as this, I think one would proceed very gently and be certain not to harm the patient above all else.

William R. Platt, M. D., St. Louis, Missouri: Dr. Diamond of Boston recently mentioned the fact that there are iatrogenic complications of steroid therapy in lymphomas and non-lymphomas and that patients treated with Cortisone (children in his series) develop hypoplasia and fatty infiltration of marrow so that one may get a reduction in size of lymph node structures, and spleen, etc., but the hematopoietic system reacts in reverse. I think this should be borne in mind in treating any lymphomatous-like state without knowing his specific diagnosis.

Dr. Block: This patient had masses in her nose and in her throat; her temperature was going up each day; she was not eating and was getting to the point where she was cyanotic, with a high respiratory rate and a high pulse rate. This is a medical emergency. Against that, the theoretical considerations of whether or not I am going to produce an aplastic bone marrow a week or a month from now does not cut any ice at all. If you look at the illustrations of Dr. Diamond's paper, you will find that the diagnosis of an aplasia of the bone marrow is based on an aspiration smear, which is no way to make a diagnosis of an empty bone marrow. This could just as easily be due to a poor specimen, and I have literally treated hundreds of patients with steroids and I have yet to see a single patient who has ever gotten an aplastic bone marrow from steroids.

Dr. Regato: I haven't seen the China Wall either.

Editor's Note: In September of 1966 the patient presented enlargement of axillary and inguinal nodes and later also a pre-auricular lymph node; for all of these manifestations she was given radiotherapy. Her last recorded examination was in April, 1967, when she had no complaints except relative nasal obstruction and recent "cold"; there were several new small enlarged nodes in the left supraclavicular region. She is now taking Prednisone and A-methopterin and does full-time work as a housewife. A radiographic bone survey has failed to show any bony lesions. She is under the care of Dr. Block whose present diagnosis is Letterer-Siwe's disease.

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10. *Lymphocytic Lymphosarcoma (?) primary undetermined*

Contributed by F. Buschke, M. D. and G. A. Jack, M. D.

San Francisco, California

THE PATIENT was a 67-year old man in June, 1965, when he complained of epigastric pain and slight loss of weight; for two years he had been relieved by an ulcer regime. Examination revealed the presence of a 1 cm lymph node in the right upper cervical region and demonstrable blood in the stools. The hemoglobin was 14.4 gm %.

Dr. Mellins: A large, somewhat undermined, ulcer crater is seen along the lesser curvature of the antrum of the stomach just proximal to the pylorus. Just caudal to the ulcer there is a 1 cm filling defect which could represent a mass, either intraluminal or intramural. The stomach is slightly larger than normal and one or two rugae in the fundus are prominent. A cluster of punctate and flaky calcification, roughly triangular in configuration, is projected just medial to the fundus of the stomach, and another similar collection is projected over the spine. The appearance is that of adrenal calcification, probably of no present clinical significance. There is compression of the first lumbar vertebra but evidence of bone destruction is lacking.

Roentgen evaluation of a gastric ulcer with a view to separating the malignant from the benign lesions requires careful radioscopic examination and many spot films. The most important finding is the presence of an associated mass. Lymphosarcoma may be separated from carcinoma by the presence of larger, uneffaceable folds in addition to the presence of a localized mass. Because both of these findings are present, I would suggest gastric lymphosarcoma. The appearance suggests penetration. Two cases of ulcerating gastric lymphosarcoma which went on to perforate have been seen at our institution.

Dr. Mellins' impression: 1.) LYMPHOSARCOMA OF THE STOMACH 2.) PSEUDOLYMPHOMA.

Roentgenologic Impressions Submitted by Mail

Gastric lymphosarcoma	52
Gastric carcinoma	25
Benign gastric ulcer	27
Vertebral metastasis	8
Others	20

Dr. Mellins: I would say that gastric carcinoma is impossible to exclude on the evidence we have. A benign gastric ulcer does not account for the mass that we see just below the ulcer. I saw no evidence for vertebral metastasis. One could see no signs of destruction of vertebral trabeculae. This vertebra was, on the contrary, more dense, indicating that the trabeculae were pushed together rather than previously destroyed.

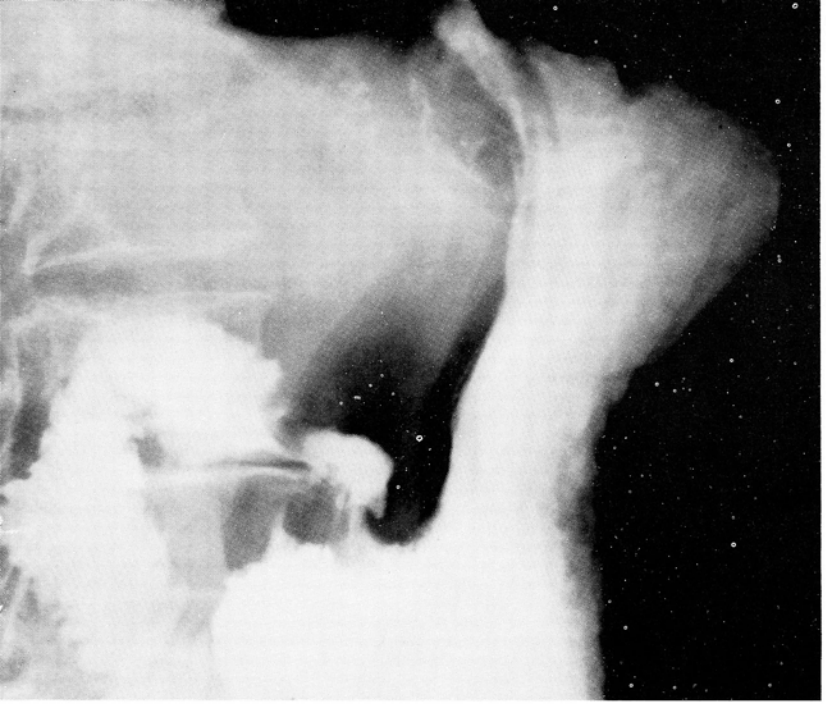

Fig. 1—Large ulcer along the lesser curvature of the stomach.

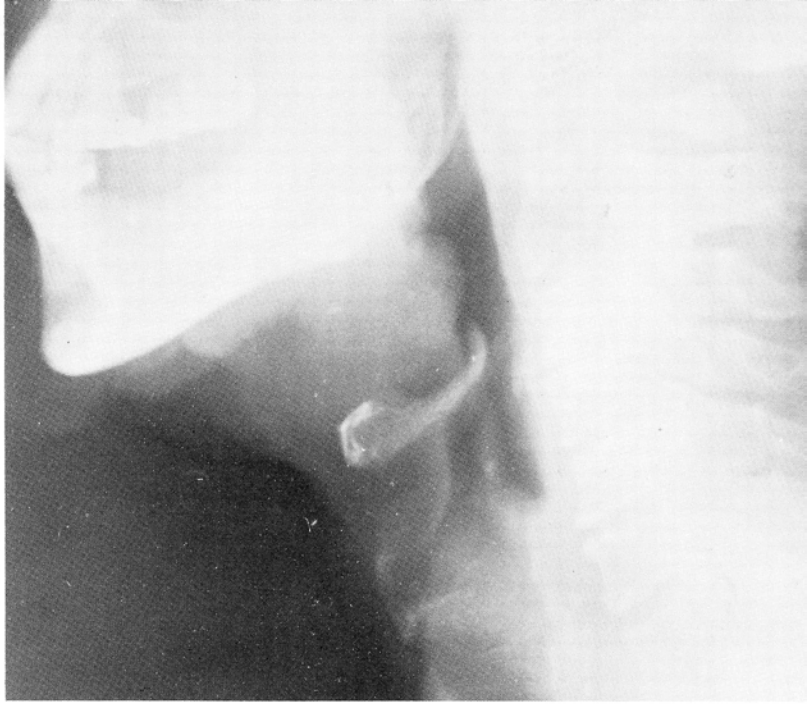

Fig. 2—Roentgenogram of the soft tissue of the neck showing obvious mass of the base of the tongue obliterating the vallecula.

Dr. Regato: Dr. P. W. Voltz, of San Antonio, and Dr. J. C. Lemon, of Denver, offered an impression of gastric lymphosarcoma; Drs. J. T. Travis, of Topeka, and Dr. R. J. Kurth, of Lackland, preferred benign gastric ulcer. Dr. N. Salerno, of Philadelphia, suggested carcinoma of the antrum.

Operative findings: On July 9th, 1965, a laparotomy revealed the presence of a perforated ulcer of the lesser curvature surrounded by an indurated area with many enlarged lymph nodes between the pylorus and the pancreas but no splenomegaly. The ulcer was sutured and gastrostomy and jejunostomy done; two lymph nodes were removed. A cervical lymph node biopsy was also done.

Dr. Rappaport: The sections of the lymph node show a complete obliteration of the architecture by a cellular proliferation that appears rather uniform at this magnification. In one area, however, one sees a preserved peripheral sinus; this should not deter one from making a diagnosis of malignant lymphoma for the reasons that I have pointed out in the discussion of Case No. 3. In some areas, a vaguely nodular pattern is evident (Fig. 3); it is accentuated by reticulin stains.

Cytologically, the predominating cell is a neoplastic lymphocyte. Great variations in nuclear size and shape are evident (Fig. 4). I interpret the sections as malignant lymphoma, poorly differentiated lymphocytic type. This is synonymous with so-called "lymphoblastic" lymphosarcoma.

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA, poorly differentiated lymphocytic type (lymphosarcoma).

Histopathologic Diagnoses Submitted by Mail

Lymphosarcoma	72
Malignant lymphoma	27
Reticulum-cell sarcoma	9
Follicular lymphoma	8
Reactive lymphoid hyperplasia	17
*Hodgkin's disease	4
Six others	20

Dr. Rappaport: The majority of the participants called the tumor lymphosarcoma, which I consider the correct diagnosis. The diagnoses of malignant lymphoma and follicular lymphoma, without designation of the cytology are not entirely satisfactory. The diagnosis of reticulum-cell sarcoma is indicative of the old problem of appreciating cell size and evaluating nuclear detail in imperfectly fixed material. I cannot quite understand the diagnosis of "reactive hyperplasia" and I do not even know how to discuss this possibility.

Dr. Regato: Dr. C. Masó, of Chicago, and Dr. D. L. Dawson, of Colorado Springs, also made a diagnosis of lymphocytic lymphosarcoma; Dr. E. C. Farkas, of Denver, preferred reticulum-cell sarcoma. Dr. D. C. Craig, of Denver, offered follicular lymphoma; Dr. M. T. O'Brien, of Fort Carson, also suggested follicular lymphoblastoma progressing to reticular, or histiocytic, lymphoma. Dr. W. Black, of St. Louis, and Sister Joseph Ignatius, of Cincinnati, preferred lymphoid hyperplasia and Dr. R. H. Stienmier, of Denver, Hodgkin's sarcoma.

Subsequent history: From August to September, 1965, the patient was submitted to radiotherapy for the remaining perigastric adenopathy. During the course of treatments, a smooth, asymptomatic mass was found in the base of the tongue and vallecula: it was irradiated, without benefit of biopsy, and regressed promptly.

In October, 1966, the patient appeared well; the gastric ulcer had healed and the lesion of the base of the tongue had disappeared.

Dr. Steinfeld: In this patient, as in all patients with malignant tumors, you need a program, and the program for a patient with lymphoma would include complete blood count, reticulum-cell count, Coombs' test, electrophoretic pattern, bone marrow, with sections done as well as smears to see whether or not there is involvement, uric acid and BUN. I think lymphangiography is superfluous in patients with lymphosarcoma and reticulum-cell sarcoma unlike in those with Hodgkin's disease.

Henry J. Caes, M. D., Sioux City, Iowa: In the slide that I received, the lymph node was subdivided by very dense fibrous trabeculae that did not look at all like the one which was projected. In between these dense fibrous bands there were clusters of lymphocytic cells comparable to the ones demonstrated: but your slides did not at all show the dense fibrous bands that my slide showed and maybe others had the same, and hence possibly the reason for making the diagnosis of adenitis instead of the lymphoma.

Dr. Rappaport: Thank you very much; I have no explanation for that.

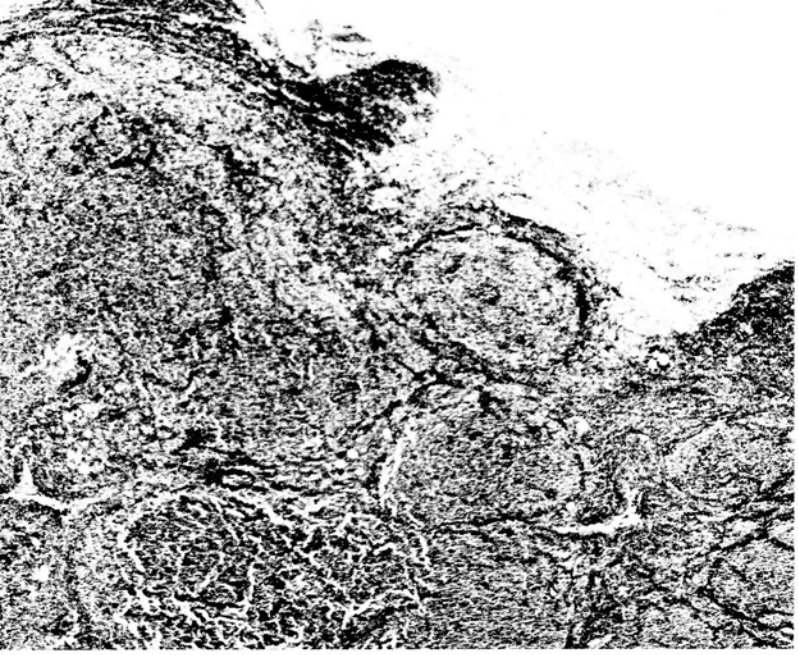

Fig. 3—Gastric lymph node showing nodular pattern. (H & E x 25)

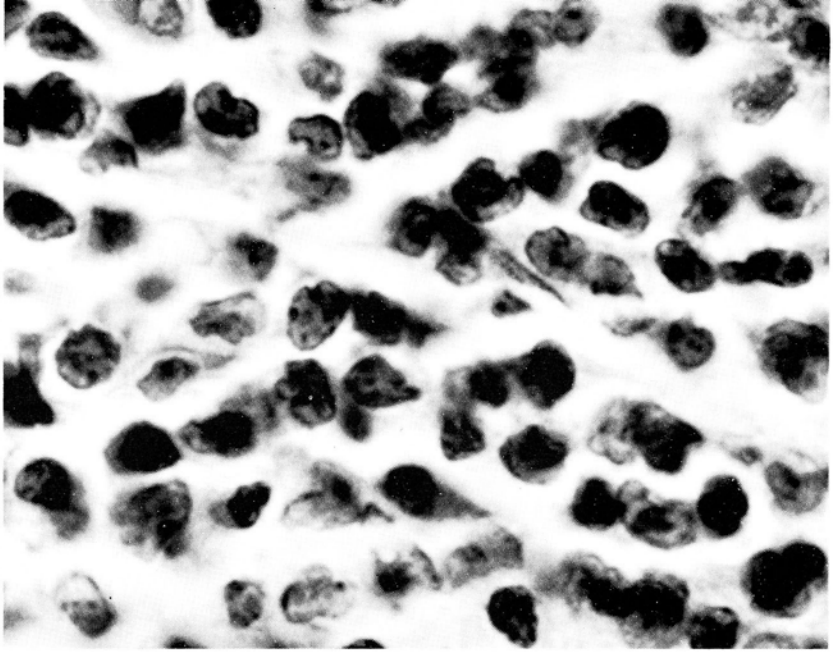

Fig. 4—High magnification of Fig. 1 showing neoplastic lymphocytes with marked variation in size and shape of their nuclei. (H & E x 1000)

Ronald Dorfman, M. D., St. Louis, Missouri: Drs. Faris and Saltzstein, of our Department, published an article, a couple of years ago, on gastric lymphoid hyperplasia simulating malignant lymphoma. I reviewed their cases with one of my radiological friends and we found that all these cases had a benign gastric ulcer, adjacent to which was a mass which was seen radiographically and which was misdiagnosed either as carcinoma or a malignant lymphoma; the mass was produced by lymphoid hyperplasia, sometimes germinal centers, frequently with plasma cells. So that the presence of an ulcer and a mass I do not think invariably means gastric lymphosarcoma; and the pathologist who receives only a small lymph node, which is not equivocally diagnostic, may then have to consider the possibility of gastric lymphoid hyperplasia associated with a benign gastric ulcer.

W. R. Platt, M. D., St. Louis, Missouri: I wonder if Dr. Rappaport might comment upon the frequent description in leterature of so-called benign lymphomas, not only of the stomach, but the lung and the rectal area. What is their ultimate outcome? Do they become truly lymphomas or are they just benign conditions to begin with?

Dr. Rappaport: Gastric lymph nodes that show reactive hyperplasia are of no help in the differential diagnosis between malignant lymphoma of the stomach and gastric ulcer with tumor-like hyperplasia of lymphatic tissue (so-called pseudolymphoma), since you can find, in patients with gastric lymphomas, lack of involvement of regional lymph nodes by the malignant disease. However, if a lymph node does show evidence of malignant lymphoma, as it did in this case, the diagnosis is much easier than it would be if you had only the gastric lesion available for study.

The term "benign lymphoma" is an unfortunate one, since it implies that we are in fact dealing with a benign neoplasm. It is uncertain, however, whether these lesions are true neoplasms or reactive tumor-like proliferations of lympho-reticular tissue. Benign lymphoid polyps of the rectum belong to this group of lesions. I believe that these and other tumor-like proliferations of lympho-reticular tissue do not progress into malignant lymphomas, although I have seen occasional instances in which so-called benign lymphoid polyps of the rectum appear to have progressed into malignant lymphoma. However, careful review of the original sections in these cases revealed that the diagnoses of benign lymphoid polyps were in error and that these were actual malignant lymphomas that had not been recognized as such in the original biopsy sections.

Dr. Regato: We are left with the fact that we can never recognize a localized malignant lymphoma from a benign lymphoma or benign proliferation because neither of them metastasizes or kills the patient; is there no other way in which we can have recourse to a confirmation of a diagnosis of benign lymphoma or benign proliferation? Is there no histologic criteria?

Dr. Rappaport: I understand your concern very well and I agree with you that survival of a patient for a long time after a stomach containing a lympho-reticular lesion has been removed does not mean that the lesion was benign. I believe that some of the truly malignant lymphomas of the stomach are curable by surgery, radiation or both. Follow-up information is not the answer to the problem in individual cases; the answer lies in careful evaluation of histologic and cytologic criteria. As I have mentioned before, the differentiation between malignant lymphoma and tumor-like proliferations of lympho-reticular tissue in the stomach is sometimes difficult, but I do not agree with those who advocate that one should depend more on the follow-up data than on the histologic features of these lesions.

I believe that there are histologic criteria for the differentiation between malignant lymphomas and benign tumor-like proliferations of lymphoid tissue and that these criteria are decisive in most cases. The fact that there are instances in which these criteria fail us merely means that we are dealing with a very difficult diagnostic problem, which is now under study in our laboratory.

Editor's Note: This patient was last examined in May of 1967. At that time he presented small discreet nodes of the axillae and groins. The CBC showed 6,100 per mm³ with 22% lymphocytes. His general condition remains good. A bone marrow biopsy has not been done.

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11. *Malignant Histiocytosis (?)*

Contributed by MERYL H. HABER, M. D.

Chicago, Illinois

THE PATIENT was a 73-year old woman in April, 1964, when her liver and spleen were found to be enlarged on physical examination. The oral temperature was 101.5° F.; the hemoglobin 9.5 gm %; the WBC 3,500 per mm³ and the serum electrophoresis normal.

Dr. Mellins: The spleen is decidedly enlarged. The lower pole is projected more than 2 cm below the left iliac crest. An indentation at the junction of the middle and lower third of the medial aspect of the spleen probably represents a normal structural indentation rather than the hilus of the spleen. Liver enlargement can not be accurately diagnosed from an antero-posterior roentgenogram of this type unless there is marked enlargement of the left lobe. There is no definite evidence of localized areas of bone sclerosis or thickening of the bone trabecula in the visualized bones. No small rounded areas of radiolucency, representing areas of myelofibrosis, are seen.

The differential diagnosis lies between myelogenous leukemia and agnogenic myeloid metaplasia. In the absence of characteristic bone changes I have no radiographic reason to favor one diagnosis over the other.

Dr. Mellins' impression: AGNOGENIC MYELOID METAPLASIA.

Roentgenologic Impressions Submitted by Mail

Lymphogenous leukemia	37
Lymphosarcoma	16
Myelofibrosis	11
Myeloma	8
Agnogenic myeloid metaplasia	5
Others	37

Dr. Mellins: I have expressed the fact that I had no way of supporting a diagnosis of leukemia or of lymphosarcoma. I certainly have no evidence for diminished bone density focally which one sees in myelofibrosis. I could not support a diagnosis of myeloma in a 73-year old individual with a spleen this size.

Dr. Regato: Dr. R. Hill, of San Antonio, also offered agnogenic myeloid metaplasia; Dr. B. Felson, of Cincinnati, and Dr. E. Salzman, of Denver, offered an impression of myelopthisic anemia, due to myelofibrosis. Dr. H. Perlman, of Philadelphia, suggested leukemia.

Operative findings: A clinical diagnosis of hypersplenism was entertained and the patient submitted to a splenectomy. During the procedure, a biopsy of the liver was done and a strip of the left leaf of the diaphragm with adjacent lymph nodes was removed. The spleen weighed 920 gm; on cut section, it was dark red in color with normal trabecular markings.

Dr. Rappaport: This is, indeed, a difficult case and I am not sure that I can give you a precise diagnosis except that there are actually only two alternatives that I have to suggest, namely: (1) a malignant lymphoma of the histiocytic type (reticulum-cell sarcoma) or (2) a malignant histiocytosis (so-called reticuloendotheliosis). From the pattern of growth I prefer malignant histiocytosis. The most characteristic feature of this disorder in the spleen is the diffuse infiltration and widening of the splenic cords by proliferating malignant histiocytes (Fig. 3). Malpighian corpuscles often are invaded by these atypical cells and may be partly or completely destroyed. Subendothelial infiltration of trabecular veins are also evident. The predominating proliferating cells are neoplastic histiocytes, some of which show evidence of erythrophagocytosis, a characteristic feature of this disease. There is an abundance of reticulin fibers; practically every cell is surrounded by delicate reticulin fibers. In the spleen, the diffuse infiltration of the pulp cords by histiocytes is characteristic of malignant histiocytosis, while the formation of well defined tumor nodules composed of neoplastic histiocytes is typical for reticulum-cell sarcoma.

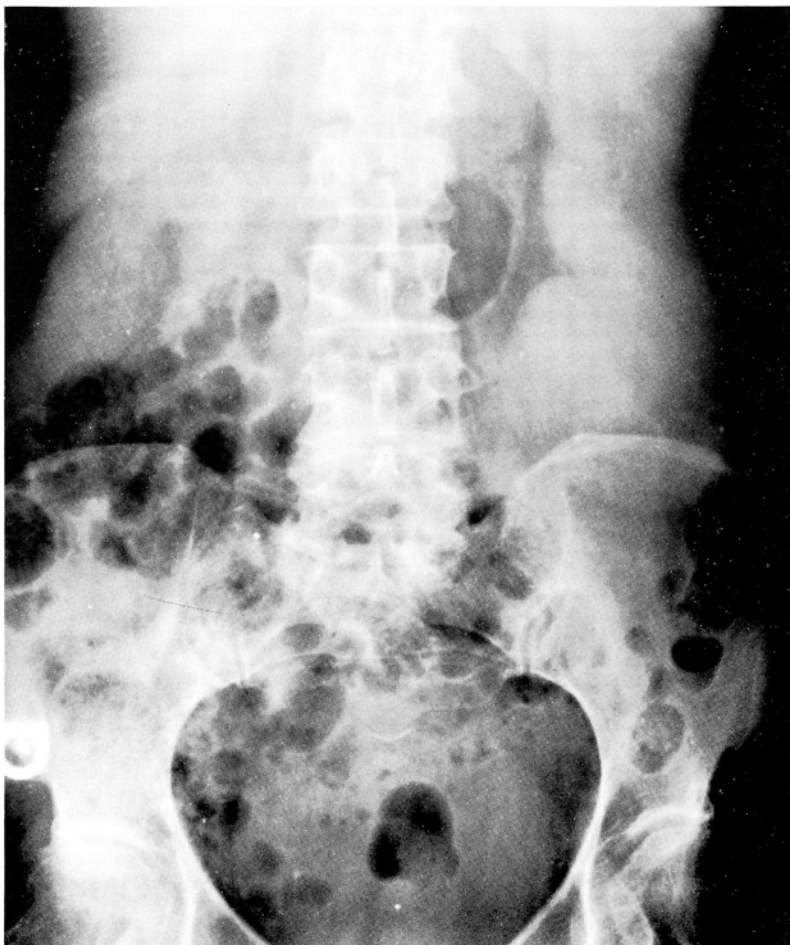
We have seen cases of "leukemic malignant histiocytosis", a rare disorder, sometimes referred to as "histiocytic leukemia". One of these was a one-year old child that clinically presented with the symptoms of a systemic disorder; there was no localized tumefaction of nodes, but splenomegaly, hepatomegaly, a petechial rash and pancytopenia were evident. The bone marrow was almost completely replaced by neoplastic histiocytes. Reticulin fibers were abundant. This patient was exceptional inasmuch as malignant histiocytes were evident in the peripheral blood (Rappaport).

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA (histiocytic type) or MALIGNANT HISTIOCYTOSIS.

Histopathologic Diagnoses Submitted by Mail

*Hodgkin's	53
Reticulum-cell sarcoma	34
Stem-cell lymphoma	10
Malignant histiocytic lymphoma	8
Acute leukemia	8
Malignant lymphoma	7
Myeloid metaplasia	17
Six others	12

Fig. 1—Roentgenogram shows the considerable enlargement of the spleen.



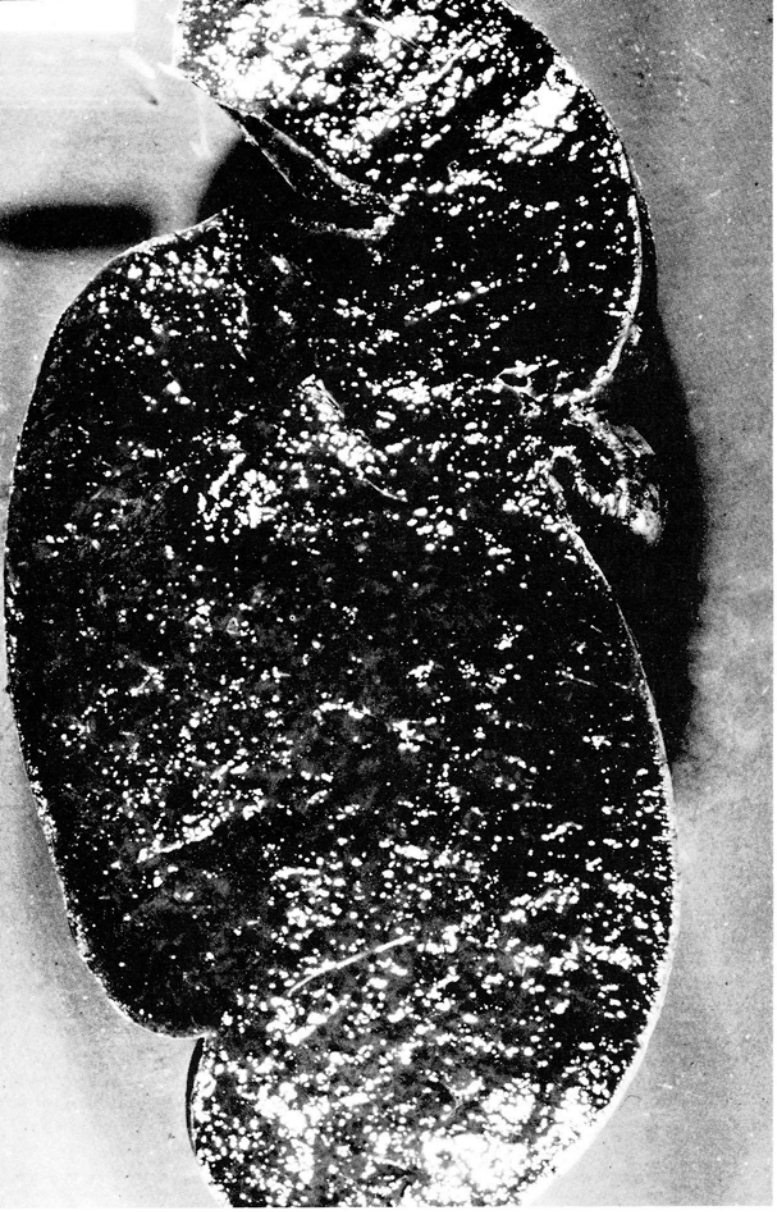


Fig. 2—Cut section of gross specimen of the spleen.

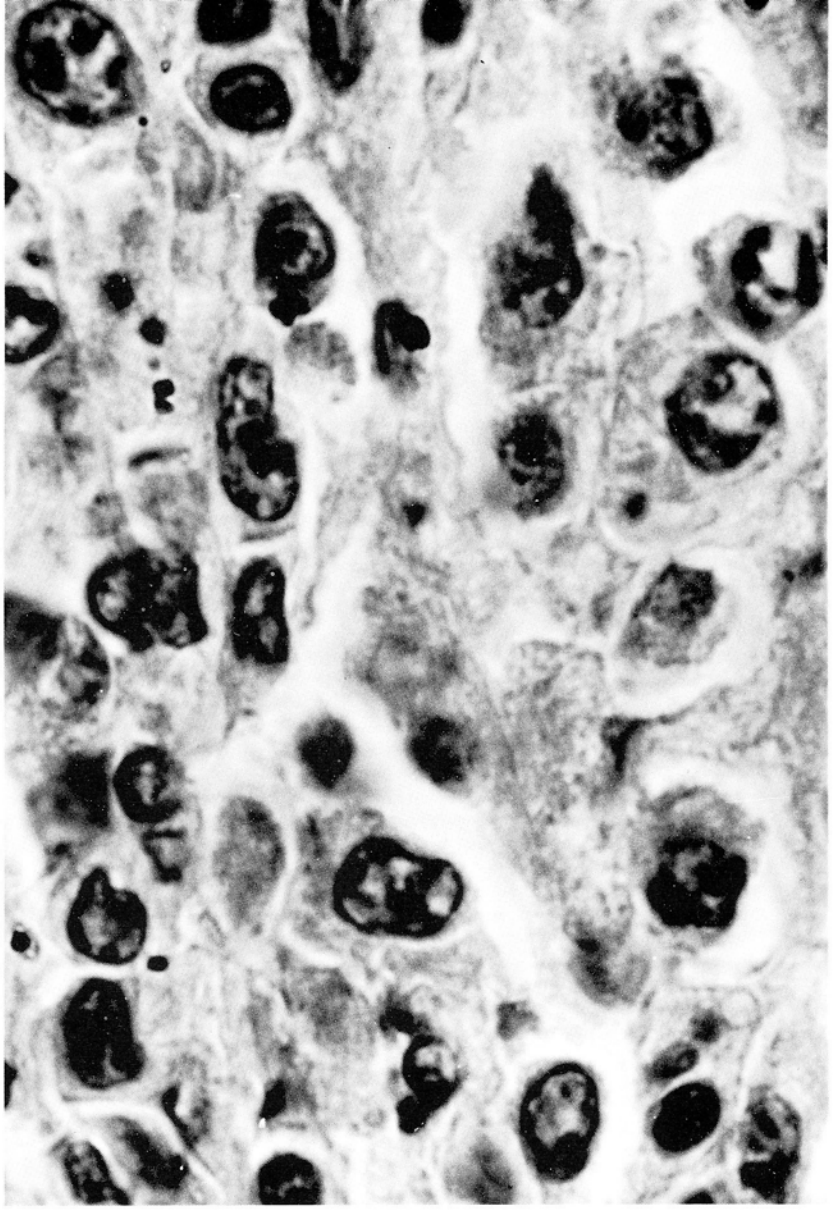


Fig. 3—Splenic cord diffusely infiltrated with neoplastic histiocytes that have abundant cytoplasm. (H & E x 1000)

Dr. Rappaport: I would not make a diagnosis of Hodgkin's disease in the absence of demonstrable Sternberg-Reed cells. Moveover, in the spleen, Hodgkin's disease does not infiltrate the pulp cords in a diffuse manner, but forms nodules that appear to arise in malpighian corpuscles. I have already discussed why I do not believe that the designation of reticulum-cell sarcoma, or of malignant lymphoma, is applicable. As to myeloid metaplasia, I found no evidence to support this diagnosis. My final diagnosis is malignant histiocytosis.

Dr. Regato: Dr. M. R. Abell, of Ann Arbor, and Dr. J. Kissane, of St. Louis, diagnosed acute monocytic leukemia; Dr. R. Delcourt, of Brussels, preferred acute myeloid leukemia; Dr. J. B. Frerichs, of El Paso, offered histiocytic, or reticulum-cell sarcoma of the spleen.

Subsequent history: On October 8th, 1965, two weeks after splenectomy, the patient died.

Dr. Rappaport: I have been wondering how a diagnosis of agnogenic myeloid metaplasia can be made on the basis of a radiologic study of the spleen without knowledge of the blood findings that are quite characteristic of this disease, such as poikilocytosis, tear-drop shaped red cells and a leuk-erythroblastic reaction. These are not recorded here.

Dr. Mellins: The rules of this game, as played here, put me in the position of making the diagnosis on the basis of statistical frequencies, and clinical sense of smell. I would say that the Roentgen method is the best method of physical diagnosis ever developed, but that is all it is! Physical diagnosis depends upon gross pathology, and with the pathologists abandoning gross pathology for the electron microscope, we must be the only ones who are interested in it. Now we have a gross pathologic change and some clinical evidence, and in order to play the game I suggested the lesion which in my clinical judgment would account for the situation. You are right that if one were to limit himself to the clinical diagnosis available, one would have to say: "splenomegaly, cause undetermined", but then you wouldn't need me.

Dr. Steinfeld: A white cell count of 3,500, a hemoglobulin of 9.5 gm %, and no platelet count given does not help us make a diagnosis of pancytopenia. I cannot make a diagnosis of hypersplenism without a very cellular bone marrow with all the normal elements represented and a patient with either persistent anemia or leukopenia with infections or thrombocytopenia and bleeding. Our experience with older people, considerably over the age of 40, who have splenectomies has been dismal. Confronted with information such as we have here, it would probably be

desirable to do a number of other tests. I think the bone marrow might give us the answer; liver biopsy might give us the answer; a splenic aspirate or splenic biopsy without doing laparotomy and splenectomy might give the answer. I would think it should be possible to get diagnostic material without resorting to a splenectomy. How to treat such a patient, however, becomes a major problem once one makes the diagnosis; but I would think that a splenectomy is a major procedure in a person of this age, and would hope that we could try to make the diagnosis by other methods.

Dr. Rappaport: The diagnosis of acute monocytic leukemia has been suggested in this case. Since acute monocytic leukemia is one of the leukemias that is most consistently associated with an elevated white blood cell count, the fact that the patient was leukopenic, would by itself, speak against this diagnosis. Also, in monocytic leukemia the individual cells have very characteristic features in tissue sections. At high magnification one sees these peculiarly indented cells. By focusing up and down one finds that many more of the cells have these monocytoid or monocytic features than is apparent at a single level. Most of the cells have kidney-shaped and indented nuclei to which Dr. Forkner, in one of his early papers, has called attention. Obviously, acute monocytic leukemia is rarely an indication for lymph node biopsy or splenectomy and, therefore, very few of us have the opportunity to see this type of case. Acute monocytic leukemia, like malignant histiocytosis, often has skin lesions, and in this respect histiocytic and monocytic proliferative diseases resemble each other. When monocytic leukemia involves the spleen, one often finds the malpighian corpuscles partially preserved. The same holds true for the granulocytic leukemias. In the differentiation between monocytic and granulocytic leukemia involving the spleen, the presence of eosinophilic myelocytes is helpful since it establishes the diagnosis of granulocytic leukemia. Otherwise, it would be difficult to differentiate between the two.

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12. *Undifferentiated Malignant Lymphoma of the Subcutaneous Tissues*

Contributed by E. Salzman, M. D., E. Johnson, M. D. and J. Eule, Jr., M. D.

Denver, Colorado

THE PATIENT was a 60-year old man in September, 1964, when he gave an 8-weeks' history of growing "lumps" on his back and abdomen. On examination there was a 12 cm subcutaneous mass in the interscapular space and a similar 7 cm mass on the abdominal wall, to the right of the umbilicus. The WBC was 8,000 per mm^3 and there was a trace of albumin in the urine.

Dr. Mellins: There is a sharply defined oval soft tissue density, slightly over 3 cm in length, projected just above the right lung root. There is no calcification or cavitation within it. The lung roots are at the upper limits of normal. The lung fields are clear. No skeletal abnormalities are seen. Ilio-pelvic and aortic lymphadenography show many of the nodes enlarged and elongated. The marginal sinuses are intact. The pattern of the lymph node architecture is that of multiple small and somewhat larger rounded areas of diminished density within the opaque area.

The nodule projected just above the right lung root could represent any benign or malignant nodular lesion within the chest. There are no findings which would permit a specific diagnosis. Since the lymphadenogram shows enlarged lymph nodes with an elongated appearance, in which the marginal sinus is intact and the distribution of the contrast medium is bead-like, the appearance is that of lymphosarcoma and the chest lesion probably represents nodular involvement by the same process. The presence of an intact marginal sinus is against a diagnosis of metastatic carcinoma and usually against the diagnosis of reticulum-cell carcinoma. I would favor a diagnosis of mycosis fungoides which has led to generalized lymphosarcomatous involvement of abdominal and thoracic lymph nodes.

Dr. Mellins' impression: MYCOSIS FUNGOIDES.

Roentgenologic Impressions Submitted by Mail

Lymphosarcoma	45
Mycosis fungoides	24
Reticulum-cell sarcoma	12
Chronic lymphogenous leukemia	8
Hodgkin's disease	7

Dr. Mellins: I am opposed to the diagnosis of reticulum-cell sarcoma on the basis of the intact marginal sinuses. Chronic lymphogenous leukemia could give these radiographic appearances and I cannot exclude it, except that it is not common to have a well-defined, almost solitary lymph node above the lung root in leukemia. Usually leukemia does not give lymph nodes of reasonable size in the chest, but rather smaller ones. Hodgkin's disease would not give a more or less peripheral lymph node this size without any lymph nodes in the lung roots.

Dr. Regato: Dr. Neal Goodman, of Denver, also made a diagnosis of mycosis fungoides; Dr. N. W. Courtney, of Ann Arbor, offered reticulum-cell sarcoma; Dr. G. S. Brown, of Colorado Springs, preferred lymphosarcoma.

Operative findings: On September 4th, 1964, the abdominal mass was excised; it was firm and reddish brown in color.

Dr. Rappaport: The section from this tumor showed a massive infiltration of the subcutaneous fat tissue with cells that cannot be identified at this magnification (Fig. 3). In the deeper soft tissues the infiltration is even more extensive, with only a few fat cells preserved. The skeletal muscle is also heavily infiltrated by these cells. At higher magnification, the predominating cells are undifferentiated with nuclei that are round or slightly indented and have a

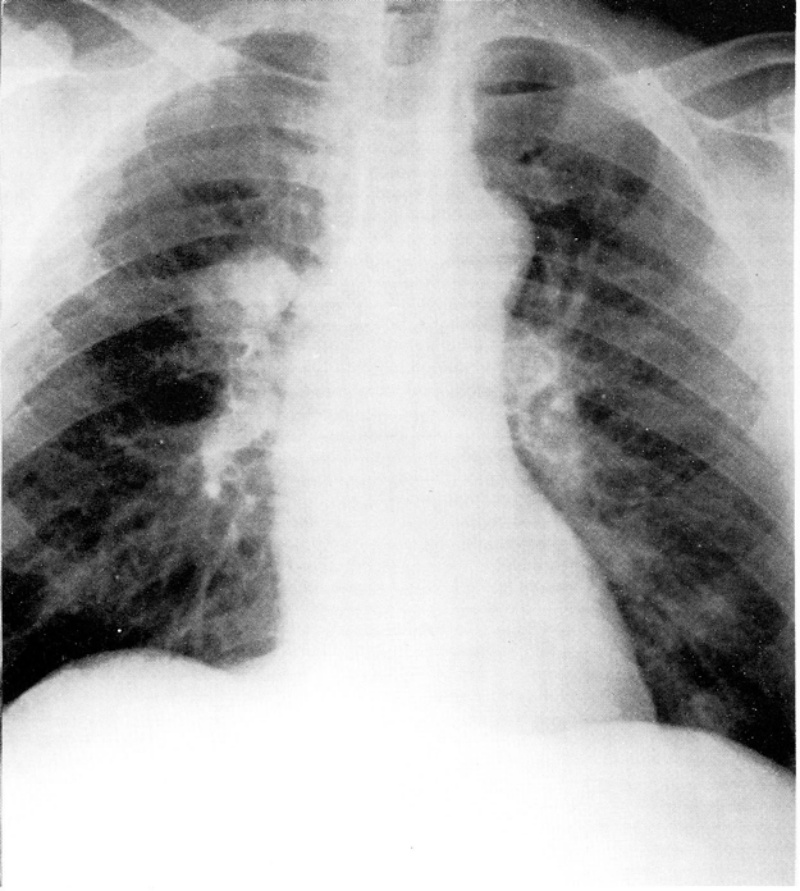


Fig. 1—Sharply defined oval soft tissue density just above the right lung root.

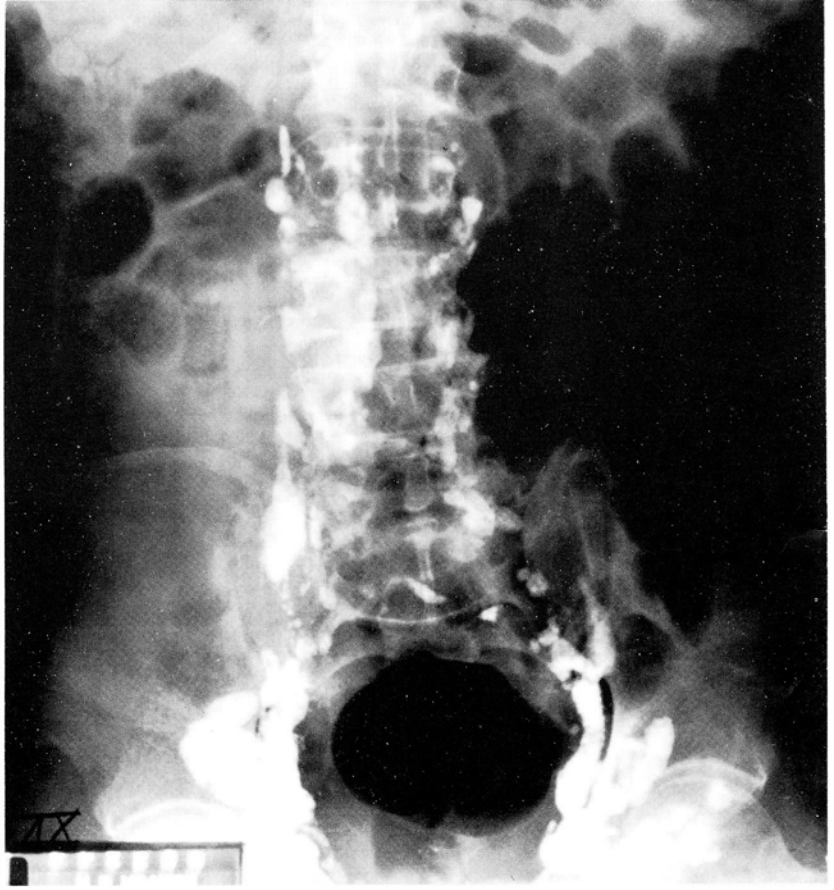


Fig. 2—Ilio-pelvic lymphadenography showing enlarged lymph nodes with intact marginal sinuses.

delicate chromatin structure (Fig. 4). Their nuclear sizes are in the range of those of macrophages that are scattered throughout the section. This suggests that this neoplasm is not a "lymphosarcoma" but either an undifferentiated or a histiocytic reticulum-cell sarcoma. Note that the reticulin fibers are scant and, because this does occur in undifferentiated reticulum-cell sarcomas, the opinion is being held by some pathologists that reticulin stains are useless. However, the production of reticulin is only one of the functions of the maturing reticulum-cell or histiocyte and it is in the less differentiated form that there may be a scarcity of reticulin fibers, as you see it here. On the other hand, an abundance of reticulin fibers, with practically every cell surrounded by them is characteristic of many of the more differentiated histiocytic reticulum-cell sarcomas. It is a feature that assists in their differentiation from anaplastic carcinomas.

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA, undifferentiated (reticulum-cell sarcoma, undifferentiated).

Histopathologic Diagnoses Submitted by Mail

Reticulum-cell sarcoma	52
Lymphosarcoma	20
Metastatic carcinoma	18
Malignant tumor, unclassified	14
Melanoma	13
*Hodgkin's disease	4
Five others	18

Dr. Rappaport: Note that the majority made the correct diagnosis of reticulum-cell sarcoma. I have already discussed why I do not believe that this is a lymphosarcoma. I did not see evidence to support a diagnosis of metastatic carcinoma but appreciate the fact that fourteen cautious pathologists in this group diagnosed a "malignant tumor, unclassified", which is sometimes a wise thing to do when dealing with an undifferentiated neoplasm. As to mycosis fungoides, I am very glad that none of the pathologists had made this diagnosis.

Mycosis fungoides is, at times, diagnosed when a malignant lymphoma involves the skin. I believe we ought to appreciate the fact that mycosis fungoides and malignant lymphoma cutis are not identical diseases, but time does not permit us to elaborate on this point and it is not really necessary, since none of the pathologists suggested this diagnosis.

Dr. Regato: Dr. H. K. Giffen, of Omaha, suggested undifferentiated bronchial carcinoma; he commented that this group of tough slides should have been accompanied by a tenderizer! Dr. G. Garay, of Memphis, suggested liposarcoma; Dr. M. T. O'Brien, of Fort Carson, preferred metastatic melanoma; this possibility was suggested by several other participants, as was a testicular primary. Dr. Sirtori, of Milan, offered reticulum-cell sarcoma.

Subsequent history: On a diagnosis of metastatic carcinoma, the patient was given radiotherapy (1,750 R in 20 days) to the interscapular mass; the irradiation was combined with 100 mg of Cytoxan three times daily and 3 mg of Prednisone twice a day. On November 1st, 1964, the mass had regressed but the patient had a serious hematemesis. A subtotal gastrectomy was done for a bleeding gastric ulcer; on November 15th, 1964, the patient expired. Autopsy revealed pneumonia with multiple abscesses, recent coronary thrombosis and lymphoid hyperplasia of lymph nodes. Testes were atrophic, otherwise normal.

Dr. Steinfeld: I think the question here might be one of therapy. There are two situations where combined therapy appears to be useful: one is the treatment of retinoblastoma with radiations and an alkylating agent such as T.E.M. interarterially, and the other is the use of Actinomycin-D and radiation, as well as surgery in Wilms' tumor. All of the other adjuvant studies are somewhat tentative, including the use of Thio-Tepa at the time of radical mastectomy for women who are post-menopausal and have positive axillary nodes. A question that I would wonder

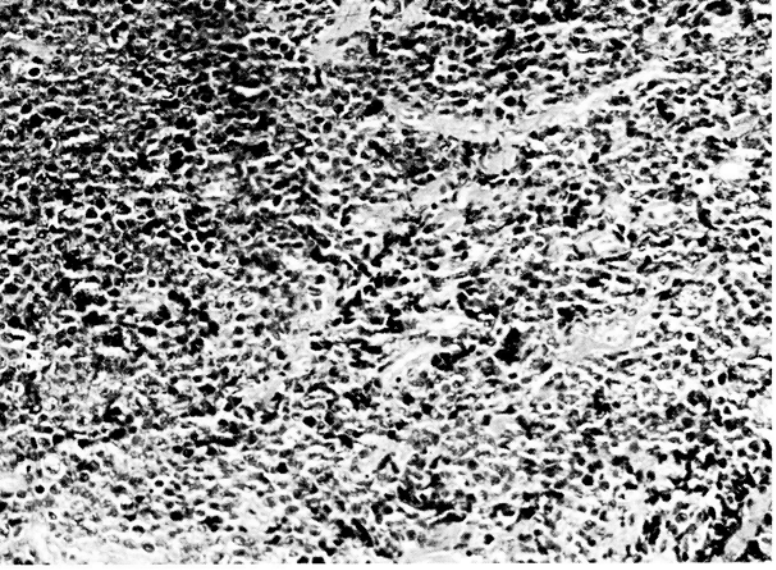


Fig. 3—Massive proliferation of undifferentiated cells that are not identifiable at this magnification. (H & E x 100)

about is whether at the time the patient bled he was thrombopenic or not; whether this bleeding was due to the ulceration alone and platelets were adequate, or whether in some way the therapy contributed to his demise.

For reticulum-cell sarcoma which is generally a disseminated disease, unless there are local problems to which you might wish to direct radiotherapy, you could consider chemotherapy alone if there were disseminated disease. But I think this depends on extent of disease which we would have to determine completely and we do not have all of that information. Presumably, the disease was localized to the areas treated with radiotherapy; but I do think we should try to relate, if we can, the final episode to whether or not platelets were depressed.

Dr. Regato: Dr. Steinfeld, the amount of radiations that this patient received would not kill a fly. Why should it kill a nice old man? Actually, he was getting some very heavy poisons and steroids that may have been responsible for his gastric hemorrhage.

Dr. Steinfeld: Perhaps radiotherapy was directed at an abdominal lesion, and the stomach was in the field irradiated. He was receiving 300 mg of Cytoxan; this is the alkylating agent with the least thrombocytopenic inducing effect, but we have seen it cause thrombocytopenia.

Dr. Regato: The amount of radiation was 1,750 R in twenty days.

Dr. Steinfeld: It is conceivable to me that he was thrombopenic but he may not have been and this may have been totally unrelated.

Robert B. Hilley, M. D., Santa Fe, N. M.: I would like Dr. del Regato to discuss permanent curability of Stage I or localized malignant lymphoma of lymph nodes, and along the same line I wonder if Dr. Rappaport would comment on whether it is possible to effect a permanent cure in a certain number of such localized areas. Does it not suggest that the pathologist should be somewhat less conservative than we have traditionally been in making diagnoses in the cases of equivocal or difficult cases?

Dr. Regato: I was reserving my remarks on this subject for the next case, but it might as well be told here because every one of these cases has had someone, sometimes quite a number of someones, making the diagnosis of Hodgkin's disease; I wanted to point out the great responsibility that the pathologist bears in making this diagnosis off-hand, in the belief that Hodgkin's disease is an incurable disease and it does not matter what poison the patient gets.

Thirty years ago when I was in my training, I knew already that one patient out of four with Hodgkin's disease, regardless of extent, could live twenty-five years in comfort. I have several patients that I treated when they were teenagers, who have become grandparents, and it is not infrequent to have patients that go for eight, ten or twelve years before their second manifestation of the disease; I have a patient on our records that went twenty-three years between his second and his third manifestation of Hodgkin's disease. This is, provided they are not killed by any poison of the day.

We have now in the field of the treatment of cancer a tremendous amount of well-meaning men, mostly hematologists and internists, who have come into the field with a lot of interest but who think of malignant tumors as peculiar cases of acute leukemias and who do not mind what kind of a poison they give the patient because the patient is going to die anyway. As a consequence, patients with Hodgkin's disease have paid with thousands of years of their collective lives to the trials of new drugs in recent years. This is not justified. To treat a young patient with his or her first manifestation of Hodgkin's by these means is a reprehensible act. Such a patient should be treated with radiotherapy and competently so; competent radiotherapy implies a little more than just "a few shots of x-rays" and "come back when you are not feeling well". I hope that answers your question.

Dr. Rappaport: I fully agree with Dr. del Regato that aggressive radiotherapy is the treatment of choice for Stage I or II Hodgkin's disease and other lymphomas and it should be carried out only by someone who has real interest and skill in the performance of this type of therapy.

I would also like to address myself to the question asked by Dr. Hilley with respect to Hodgkin's disease. "Should the pathologist, in view of the fact that missing a diagnosis may mean the difference between life and death, become less conservative?" My answer to this is: he should not become less conservative but more accurate, and there are methods whereby increased accuracy can be achieved. These are: (1) proper processing of the submitted tissue in order that the technical quality of the sections can be outstanding; (2) cutting of numerous sections through the block when there is a problem of finding typical Sternberg-Reed cells in a case of suspected Hodgkin's disease; this is the main area where difficulties will arise, because so often the inflammatory component of Hodgkin's disease is so much more prominent than the neoplastic one and (3) doing a repeat biopsy when the diagnosis is in doubt. However, there is, without any doubt, an irreducible minimum of cases of Hodgkin's disease that can not be diagnosed readily from sections submitted to the pathologist. One of the reasons may be that in certain instances of abdominal Hodgkin's disease only superficial lymph nodes are available for study and these do not show the characteristic histologic picture. In such cases, the clinician has to decide whether or not he will obtain a diagnostic biopsy by exploratory laparotomy. Apart from this possibility, I believe that when the clinical evidence for Hodgkin's disease is very strong and the histologic picture only suspicious of, compatible with or suggestive of the disease, the clinician has the responsibility of deciding how to proceed. This decision will have to be based on clinical judgment in the light of the pathologist's report. This problem will occur in a very small number of cases and must be dealt with on an individual basis.

Dr. Regato: I would like to point out that if you do proper examination of the patient, including thorough lymphangiography, you are going to find that many patients who come with their first manifestation have already another hidden one. That will be in my books no excuse

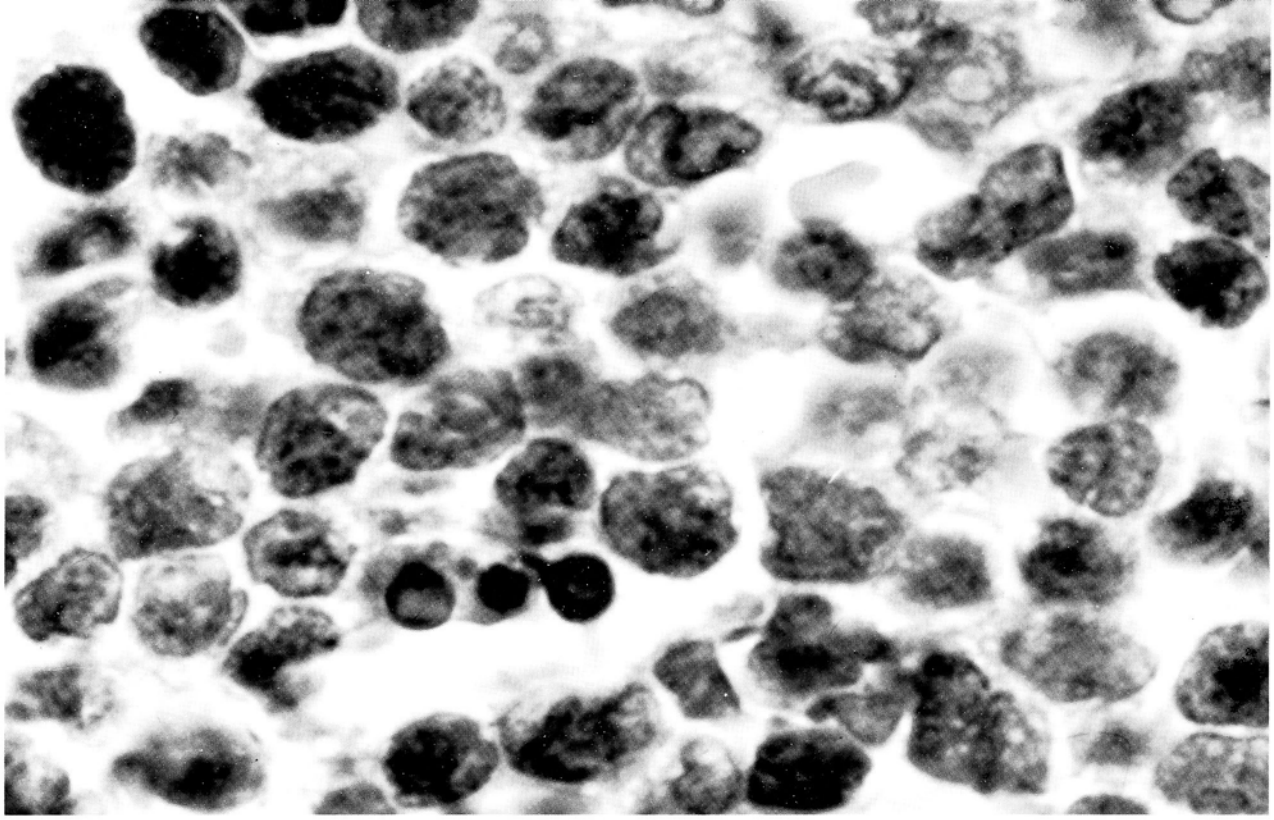


Fig. 4—The tumor cells have relatively little cytoplasm and large nuclei with evenly distributed chromatin. They are interpreted as primitive reticular cells (so-called stem cells). (H & E × 1000)

to give this patient chemotherapy. This patient should be extensively irradiated including intermediate areas that are not apparently involved. That is what we call, and we have called for many years, "prophylactic irradiation of potential areas of involvement"; when you do this, very frequently you have patients who go eight and ten years before they have another manifestation of the disease and then you treat them equally well and they go for another long period. This is not always the case, but if you treat them all this way one patient out of four may live twenty-five years.

Another thing that requires emphasis, and I think it behooves most of you pathologists, is the fact that the new generation of students and of young physicians cannot possibly understand what is involved in the field of Hodgkin's disease when they are getting everywhere a tremendous proportion of misdiagnosed cases of Hodgkin's disease that contribute to establish an erroneous judgment as to what the prognosis of this disease is.

Dr. Steinfeld: Hematologists also feel that the treatment of choice for Stage I, Stage IIA, and some patients with Stage IIB and III with the new classification is radiotherapy. I think there is no question about this.

J. Eule, Jr., M. D., Denver, Colorado: This man had arthritis for many years; for twenty or so years he had been on Prednisone and various steroids for his arthritis. I think this was the reason for that; not part of the treatment of this disease. In answer to Dr. Steinfeld's question about the further hematology, there were several counts that showed slightly to greatly decreased platelets at the time he came in with the hemorrhage.

W. J. Frable, M. D., Richmond, Virginia: I wonder if I could ask Dr. del Regato a question concerning the response to radiotherapy to be expected in Hodgkin's disease. We are confronted at the Medical College at this time with a 10-year old child, the daughter of a surgeon, who has a mediastinal mass and cervical adenopathy; we have a biopsy of a node which we feel very strongly is Hodgkin's disease. This child has received radiotherapy for only one week and, to the consternation of the radiotherapist, the mediastinum has cleared up completely and the cervical adenopathy has disappeared. He is so concerned about this response that he now questions the diagnosis of Hodgkin's disease.

Dr. Regato: A diagnosis of Hodgkin's disease in children of that age should be taken with great caution. There are possibilities of pitfalls in that diagnosis and I would want first to make sure that this is the case. It is true that there is a relative difference in radiosensitivity. A tumor that does disappear rapidly is more likely to be a leukemic mass or a lymphosarcomatous mass than Hodgkin's disease. On the other hand, depending on the individual, the response might be different, so I would not say that that in itself rules it out. What should rule it out is a good histopathologic re-investigation of the diagnosis.

Dr. Frable: Dr. Saul Kaye rendered this diagnosis and he has sent slides to Dr. Rappaport in the past and he feels sure enough about this case that he would not bother him with it. In your opinion, would this be a very unusual response.

Dr. Regato: I would not say it is very unusual; in the average Hodgkin's disease that we see the response is less prompt than that of a lymphosarcomatous mass and this one somewhat less than that of a leukemic mass; but this is only relative. They are all radiosensitive and potentially radiocurable in situ.

13. *Lymphosarcoma of the Mediastinum*

Contributed by L. I. Gottleib, M. D.

Salt Lake City, Utah

THE PATIENT was a 5-year old girl in October, 1965, when she presented with a periorbital edema of 2 weeks' duration which rapidly spread to the rest of the face and neck. On examination the child was dyspneic, mildly cyanotic and presented evidence of collateral circulation on the anterior chest wall.

Dr. Mellins: There is a lobulated mass extending approximately equally to both sides of the midline in the superior mediastinum. The mass does not extend above the clavicles nor is there evidence of involvement of the lung fields. There is no evidence of calcification. The bone pattern is normal. Tuberculous adenitis, ectopic thyroid gland and ectopic parathyroid gland produce decidedly smaller masses than in the present case. A cystic hygroma is usually situated in the lower half of the retrosternal region and presents a well circumscribed circular or oval appearance. A dermoid would not be expected to give a lobulated outline and often calcification can be seen within it. The lobular quality and the symmetrical position is likewise against a bronchogenic cyst. The appearance is that of a lymphosarcoma probably arising in mediastinal lymph nodes but a thymic origin cannot be excluded. Superior venacava obstruction by lymphosarcoma occurs about four times as commonly in children as in adults.

Dr. Mellins' impression: LYMPHOSARCOMA of the mediastinum, producing a superior venacava syndrome.

Roentgenologic Impressions Submitted by Mail

Malignant lymphoma	61
Leukemia	27
Thymoma	20
Teratoma	8
Others	7

Dr. Mellins: A symmetrical lobulated lesion of this kind is not common in leukemia and is common in lymphosarcoma. I could not exclude a thymic origin to this mass but thymoma does not generally produce a lobulated lesion of this kind. I do not have any of the things to go along with teratoma and the appearance of the symmetrically lobulated midline lesion certainly suggests lymphosarcoma without much question.

Dr. Regato: Most of the participating radiologists met on an impression of lymphosarcoma or reticulum-cell sarcoma; a few suggested lymphogenous leukemia.

Operative findings: On October 26th, 1965, the patient was taken to the operating room. She had bronchial spasm and cardiac arrest at the initiation of the anesthesia but recovered. Anterior thoracotomy was done through the sternum. A large tumor extending from the neck to the pericardium was found surrounding all mediastinal structures; it had to be dissected from the superior vena cava, the innominate vein and both the subclavian veins. About 1/10th of the tumor could not be removed. The specimen weighed 260 gm and consisted of grayish pink tissue. The largest fragment was 12 x 8 x 7 cm; the tissue appeared loculated; rather homogeneous, with focal areas of hemorrhage.

Dr. Rappaport: At low magnification, one can identify thymic tissue that has been invaded by the neoplasm. One also can see residual Hassall's bodies in areas where the tumor has invaded the thymus extensively. In other areas, portions of uninvolved thymus are still evident. This preservation of thymic tissue is remarkable in view of the fact

Fig. 1—Lobulated mass in the midline of the superior mediastinum.

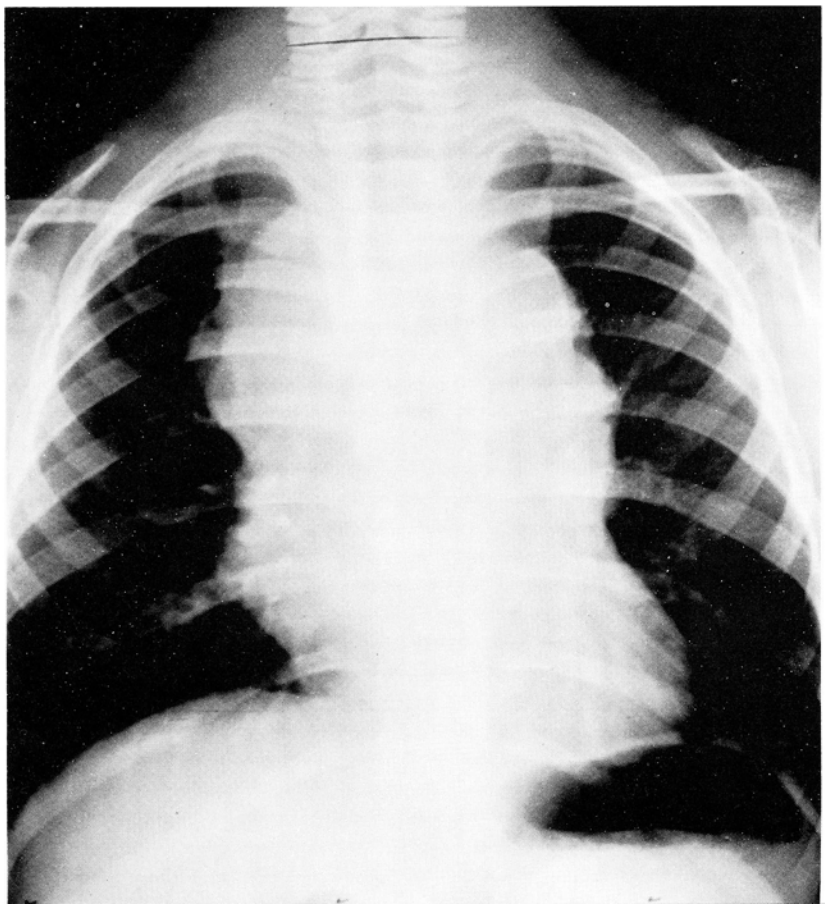
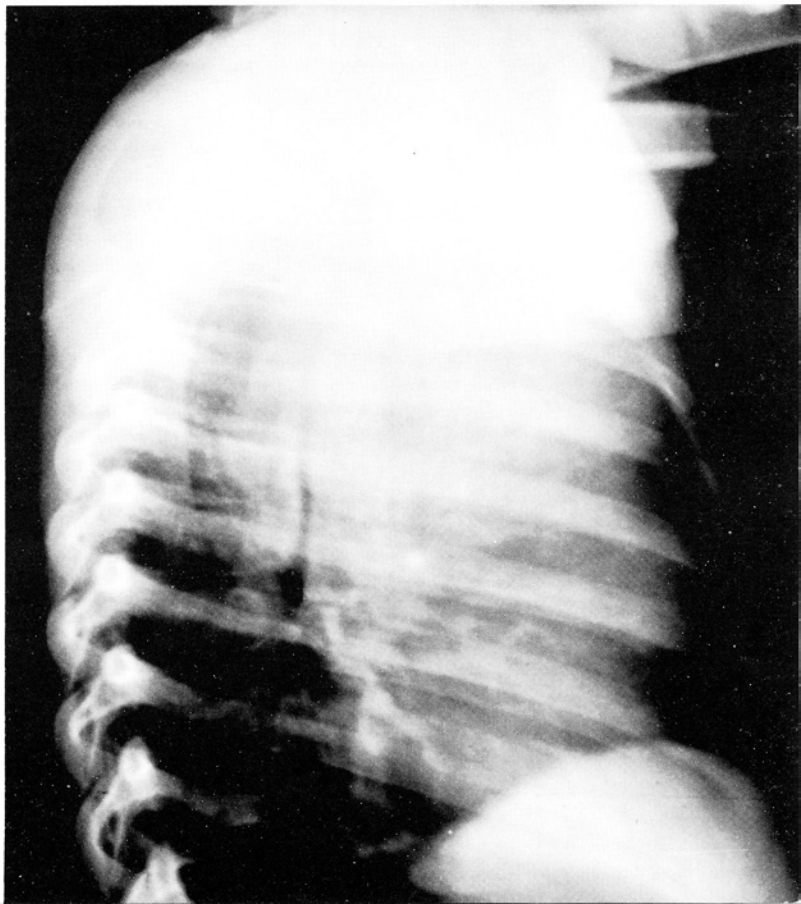


Fig. 2—Lateral roentgenogram showing no posterior invasion.



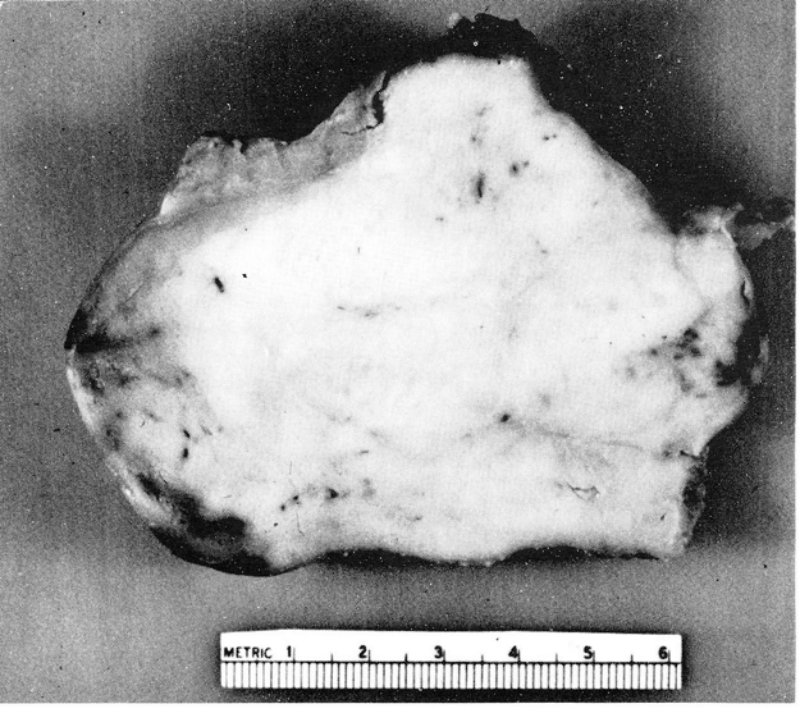


Fig. 3—Cut section of surgical specimen showing rather homogeneous structure with small areas of hemorrhage.

that the involvement of the anterior mediastinum was as massive as has been shown to you by Dr. Mellins. Now the question arises: has the tumor originated from the thymus or has it arisen in parathymic lymph nodes and invaded the thymus secondarily? Although this cannot be answered with certainty from the evidence that we have, the observation of partially preserved thymus in as large a tumor as described in the radiologic and operative findings, would tend to suggest origin outside the thymus. At high magnification, a predominantly lymphocytic neoplastic proliferation is evident. The nuclei of the predominating cells are appreciably smaller than those of histiocytes that are evident in the same field (Fig. 4). This is of assistance in establishing the predominantly lymphocytic character of this neoplasm, which I interpret as malignant lymphoma, poorly differentiated lymphocytic type, or lymphosarcoma, of the anterior mediastinum.

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA, poorly differentiated lymphocytic type (LYMPHOSARCOMA).

Histopathologic Diagnoses Submitted by Mail

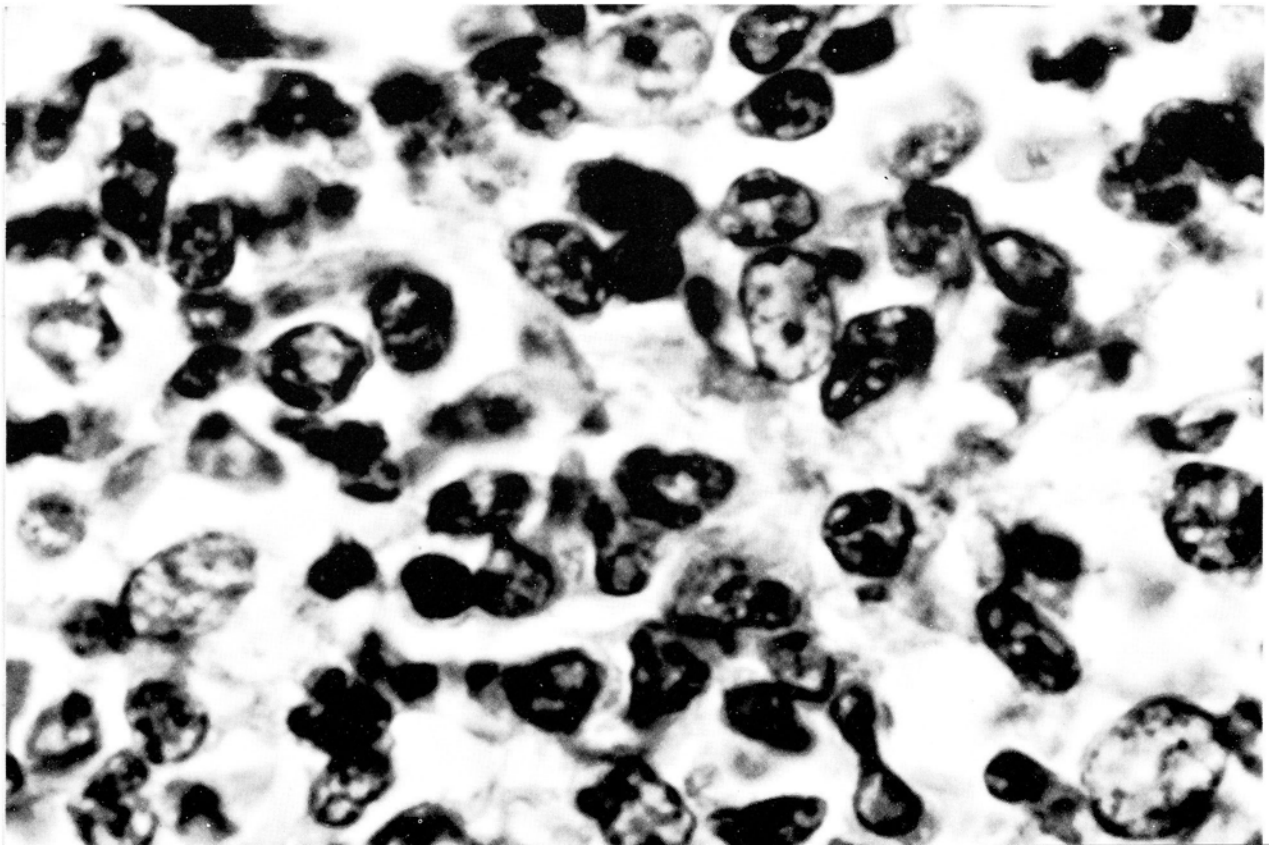
Lymphosarcoma	65
Malignant lymphoma	34
*Hodgkin's disease	12
Lymphogenous leukemia	15
Burkitt's	6
Thymoma	46
Four Others	8

Dr. Rappaport: The majority of the pathologists made a diagnosis of lymphosarcoma or malignant lymphoma. The diagnosis of "lymphogenous" leukemia is not supported by the histologic findings nor by the available data. However, children with lymphosarcoma often have circulating tumor cells that may reach leukemic proportions. These "lymphosarcoma cells" differ, cytologically, from the lymphoblasts or stem cells of acute childhood leukemia. Surprising is the large number of pathologists who suggested the diagnosis of thymoma. This diagnosis should not be made in the presence of an identifiable malignant lymphoma even when it is believed to have arisin in the thymus, for which there is no proof in this case. I believe that the diagnosis of thymoma should be reserved for thymic tumors that have an epithelial component.

Dr. Regato: Dr. M. R. Abell, of Ann Arbor, made a diagnosis of "leukemic thymoma" or of leukosarcoma; Dr. J. D. Bauer, of St. Louis, and Dr. E. Murphy, of Mexico City, suggested a Burkitt's tumor. Dr. W. J. Frable, of Richmond, Virginia, preferred Hodgkin's.

Subsequent history: The patient was given post-operative radiotherapy from November 1st to November 30th, 1965, with a total dose of about 2,690 R at the mid plane of the mediastinum in 30 days.

Fig. 4—The predominating tumor cells are neoplastic lymphocytes showing marked nuclear variation. The nuclear chromatin is coarse and irregularly arranged. Several histiocytes are evident. Their pale vesicular nuclei are considerably larger than those of the predominating neoplastic lymphocytes. Whether they are neoplastic or non-neoplastic histiocytes is difficult to establish. Some of them show evidence of phagocytosis. (H & E x 1000)



In January, 1966, the patient presented generalized adenopathy and she was treated with Vinblastin with some regression followed by recurrences. She became debilitated and dyspneic and expired on March 27th, 1966, with widespread manifestations. No autopsy was done.

Dr. Steinfeld: For a poorly differentiated lymphosarcoma, our choice of drugs would be similar to that for reticulum-cell sarcoma, Cyclophosphamide or Vincristine; Prednisone may cause regression in a fair number of these patients. If the tumor appeared to be blastic, then the patient would be treated as if she had acute leukemia and they may respond to Methotrexate or 6-Mercaptopurine.

L. I. Gottlieb, M. D., Salt Lake City, Utah: I think the diagnosis that my colleagues made on this case was Hodgkin's disease. The child had leukopenia and 10% eosinophilia in the peripheral count on admission. In addition to this, we were somewhat impressed by the foci, almost small abscesses of eosiniphils. I wonder if Dr. Rappaport has any comment on this finding in the case?

Dr. Rappaport: I do not believe too much significance should be attached to the accumulation of eosinophils in lymphomas of patients who have eosinophilia. Eosinophilia may be due to causes unrelated to the lymphoma, such as parasitism or allergic phenomena. I could not identify Sternberg-Reed cells in this tumor, not even cells that resembled them. Moreover, the lymphocytes in Hodgkin's disease are mature appearing and quite different from the atypical forms that predominated in this tumor.

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14. Undifferentiated Malignant Lymphoma Or Acute Stem-Cell Or Lymphoblastic Leukemia?

Contributed by R. M. Nalbandian, M. D., J. Farah, M. D. and M. Striecheli, M. D.

Royal Oak, Michigan

THE PATIENT was a 9-year old boy in September, 1964, when he presented with a recent swelling of the right wrist and of both ankles, accompanied by slight fever of 101° F. The hemoglobin was 13 gm %; there were 12,000 WBC per mm³ with normal differential; the ASO Todd titer was 166 units and the EKG was normal.

Dr. Mellins: Bone destruction involving the basal metaphyses of many of the distal and middle phalanges of both hands is seen. The zone of provisional calcification is retained. Similar changes are noted in the distal metaphysis of the right third metacarpal and the left second metacarpal. Focal areas of osteolysis are seen in several carpal bones. Minimal periosteal new bone formation is seen along the lateral aspect of the right third metacarpal bone.

Focal lytic lesions occur in sickle cell anemia. The children are very young and there is evidence of considerable anemia and soft tissue swelling. Periostitis is usually more extensive. The presence of some normal metaphyseal junctions as well as the persistence of the zone of provisional calcification are against the diagnosis of rickets and the absence of generalized demineralization of bone and more extensive periosteal change are against the diagnosis of scurvy. Chondro-osteo-dystrophy would likewise be more generalized. The clinical presentation as a case of acute rheumatism, but without subsequent laboratory data to support this diagnosis, always suggests the possibility of acute leukemia. The findings are those of invasion of the growing ends of the bones by leukemia cells. Permeation of the cortex leads to periosteal irritation and new bone formation. Persistence of the zone of primary calcification is a characteristic finding.

Dr. Mellins' impression: ACUTE LEUKEMIA, (aleukemic phase).

Roentgenologic Impressions Submitted by Mail

Leukemia	68
Hand-Schüller-Christian's	9
Sarcoidosis	8
Others	40

Dr. Mellins: The radiologists favored a diagnosis of leukemia. The involvement of the metaphysis in this widespread way—it is not in my experience the common location for Hand-Schüller-Christian disease nor is permeation of the cortex. Sarcoidosis does not produce an appearance in the metaphyses; it is not common in children and when it is present it produces a rather circular punched out area at the distal ends of the phalanges, rather than this permeated appearance at the base.

Dr. Regato: Dr. J. C. Lemon, of Denver, suggested Hand Schüller-Christian's disease; Dr. S. Lee and N. Pliskin, of Philadelphia, offered Still's disease; most others preferred a diagnosis of leukemia.

Operative findings: A diagnosis of rheumatoid arthritis was made and the patient treated with salycilates; there was a rapid recurrence of pain and swelling and he was given steroids. Roentgenograms showed lesions in other bones. A bone marrow biopsy was reported as showing "accelerated erythrogenesis, predominantly normoblastic, with 9% stem cells". On November 2nd, 1964, a segment of the left fibula was removed for histopathologic examination.

Dr. Rappaport: This remarkable biopsy specimen shows a very interesting pattern that has been referred to as so-called "starry sky" pattern (Fig. 3). It occurs in germinal centers of reactive follicles, but is also characteristic of the undifferentiated malignant lymphomas of the Burkitt type reported in African children. Because of their poor quality, the sections were difficult to photograph at high magnification. For the same reason, nuclear structure was difficult

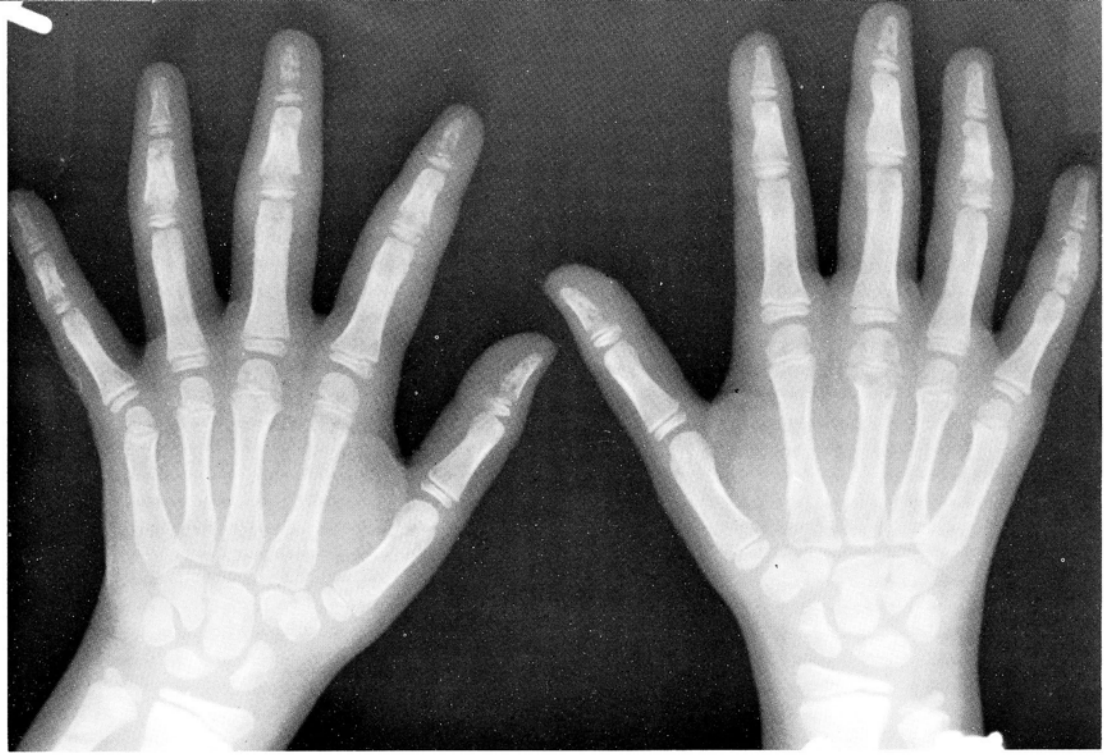


Fig. 1—Bone destruction of many of the basal metaphyses of the distal phalanges.

to appreciate (Fig. 4). The tumor cells were relatively large, about in the order of the size of identifiable histiocytes in the same fields. I interpreted them as undifferentiated or stem cells, and therefore I made a diagnosis of "malignant lymphoma, undifferentiated", and added "Burkitt's type", although I wish now that I had not added this eponym. A kodachrome of a lymph node imprint was kindly provided by Dr. Nalbandian just before this afternoon's session and was not available to me earlier. The tumor cells are indeed undifferentiated or "blast" cells and they have many vacuoles similar to those that have been reported in the malignant lymphoma of the Burkitt type. The vacuoles in Burkitt's lymphoma are sudanophilic and it is not known how the tumor cells acquire this readily demonstrable lipid material. Similar cytoplasmic vacuoles have also been observed in acute lymphoblastic leukemias of childhood.

I made a diagnosis of malignant lymphoma, undifferentiated type. However, I cannot reconcile this diagnosis with the roentgenologic findings, which are much more suggestive of an acute leukemia of childhood, and I believe this diagnosis has to be seriously considered. I do not know how it can be definitely established from the available clinical and laboratory data and without examination of bone marrow smears.

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA (undifferentiated type).

Histopathologic Diagnoses Submitted by Mail

Ewing's sarcoma	37
Reticulum-cell sarcoma	28
Burkitt's tumor	15
Malignant lymphoma	18
Lymphosarcoma	16
Leukemia	22
Histiocytosis	18
*Hodgkin's disease	0 !
Nine others	25

Dr. Rappaport: I would find it very difficult to go along with the diagnosis of Ewing's sarcoma; had I thought of it, I would have done a periodic acid Schiff stain because, according to recent reports, Ewing's sarcoma contains PAS positive material in the tumor cells. Reticulum-cell sarcoma is a diagnosis which, when applied to the undifferentiated form, is correct; a few pathologists were impressed sufficiently with the cytology and the pattern that they felt that they could make a diagnosis of Burkitt's tumor. Malignant lymphoma is correct, such as it is, without further commitment. I would say that this is not the ordinary lymphosarcoma of childhood. An acute stem-cell or acute lymphoblastic leukemia of childhood is a diagnosis to be seriously considered and probably is the correct diagnosis. I would not consider histiocytosis.

Dr. Regato: Dr. Leo Lowbeer, of Tulsa, offered a diagnosis of Ewing's tumor; Dr. J. Kissane, of St. Louis, preferred "African lymphoma"; Dr. V. M. Arean, of Miami, and Dr. D. B. Hackel, of Durham, reticulum-cell sarcoma; Dr. D. L. Dawson, of Colorado Springs, sided with acute lymphoblastic leukemia.

Subsequent history: The patient was treated with 6-Mercaptopurine with slight improvement, but the pain persisted. In December, 1964, he was changed to Cytoxan. In February, 1965, his hemoglobin was 7.5 gm %, he presented marked petechiae, enlarged liver and spleen, and cervical lymphadenopathy. The hemoglobin and platelets remained low in spite of transfusions; the differential blood cell count showed 2% blast cells; roentgenograms revealed bone lesions of the pelvis, femurs and humeri. The patient expired on March 10, 1965.

Dr. Regato: This is the only case in the entire Cancer Seminar that did not receive a diagnosis of Hodgkin's disease by someone or other.

Dr. Steinfeld: Burkitt's lymphoma when treated with what would be otherwise inadequate doses of chemotherapy may be cured. Dr. Burkitt has treated patients and they have lived from one to five years with no evidence of recurrence after receiving one dose of 30 mg per kilo of Cytoxan. A few patients have received a second such dose and no further chemotherapy.

Regarding the treatment of acute leukemia of childhood, the treatment of choice which would result in complete remissions in over 85% of patients would be a combination of Prednisone and Vincristine, or a combination of 6-Mercaptopurine and Prednisone. After the complete remission has been achieved, the patients are maintained on a dose of Methotrexate of 15 mg per meter squared, twice a week.

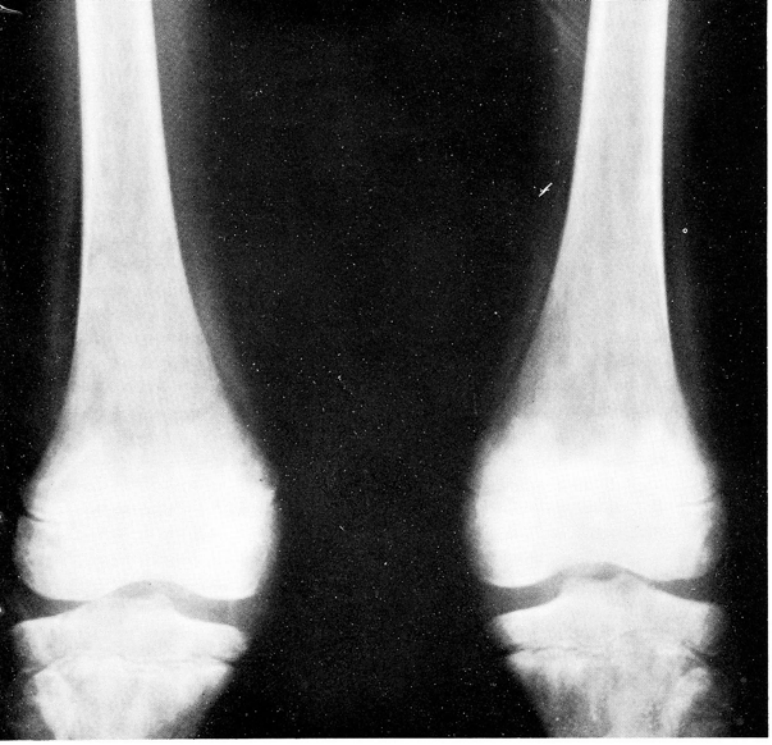


Fig. 2—Roentgenogram of both femurs showing areas of bone rarefaction in distal metaphyses.

Dr. Regato: We should not forget that what Dr. Burkitt described is a lesion which, in Africa, occurs primarily in the lower jaw of children three to ten years of age. What our pathologists have done is to identify this African entity with morphologic characters which they also find in this country, but seldom in the jaw or not necessarily in children. We question that this is the same thing as described by Dr. Burkitt.

Dr. Steinfeld: I did not suggest that this is what this patient has.

Robert M. Nalbandian, M. D., Royal Oak, Michigan: I would like to ask Dr. Rappaport if he would accept a diagnosis of aleukemic reticuloendotheliosis, and whether or not he uses that term. This child died rather rapidly without ever having any leukemic manifestations in the blood.

Dr. Rappaport: I use the term malignant histiocytosis synonymously with and instead of "aleukemic reticuloendotheliosis" because it is a predominantly histiocytic proliferative disease. This diagnosis is not applicable here because the proliferating cells are undifferentiated or "blast" cells and not histiocytes. It is either a malignant lymphoma of the undifferentiated type or an aleukemic "stem-cell" leukemia. I cannot tell which of the two it is because of the poor histologic material that I have. We do not need to have leukemic cells in the peripheral blood to make a diagnosis of acute childhood leukemia when the bone marrow picture is conclusive.

Ronald Dorfman, M. D., St. Louis, Missouri: We have critically revised malignant lymphomas *in children* in the United States and it is becoming increasingly obvious that there are cases showing clinical, pathological, histological, cytological and ultra-structural features of the Burkitt tumor. However, the "starry sky" pattern is by no means characteristic of the Burkitt tumor. It has been described in 10% of reticulum-cell sarcomas reviewed at the Armed Forces Institute of Pathology. I have been looking for it and I have found it in cases of chronic lymphocytic leukemia in adults. I believe that this is a manifestation of karyorrhexic cells undergoing mitosis or being phagocytosed. It is not a specfiic finding on which one can make the diagnosis of a tumor syndrome and this, unfortunately, is what is happening. People are seeing a few histiocytes scattered in a malignant lymphoma and are calling this "Butkitt's tumor." That is completely unwarranted.

Dr. Regato: Thank you very much, Dr. Dorfman. Without being a microscopist, that has been my concept all along.

Dr. Rappaport: I am glad that you pointed this out, Dr. Dorfman, and I am in full agreement with your comment. I have not seen the "starry sky" pattern in chronic lymphocytic leukemia but I did see it in acute lymphoblastic leukemia of childhood and in other malignant lymphomas. However, the diagnosis of undifferentiated malignant lymphoma is not suggested on the basis of the "starry sky" pattern alone. It is suggested on the basis of the predominance of undifferentiated cells that cannot be classified as lymphoblasts and may represent neoplastic primitive reticular cells. I believe that we all agree on that point. However, I would like to ask both Drs. Dorfman and Block whether they believe that this is an undifferentiated malignant lymphoma or acute leukemia of childhood and whether it is possible to make a decision from the histologic material and the clinical data available in this case.

Fig. 3—The bone marrow is extensively replaced by cellular proliferation that presents the so-called "starry sky" pattern. (H & E x 40)

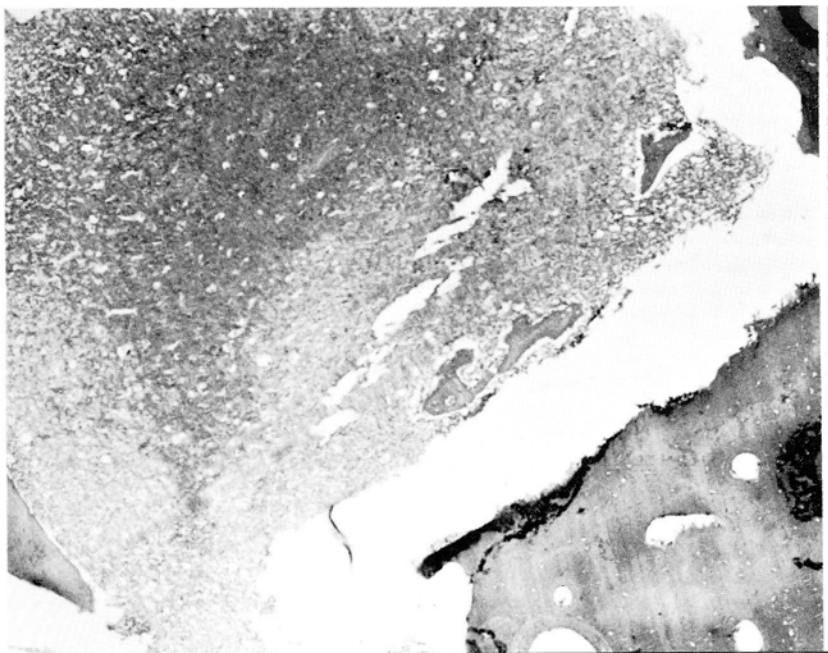
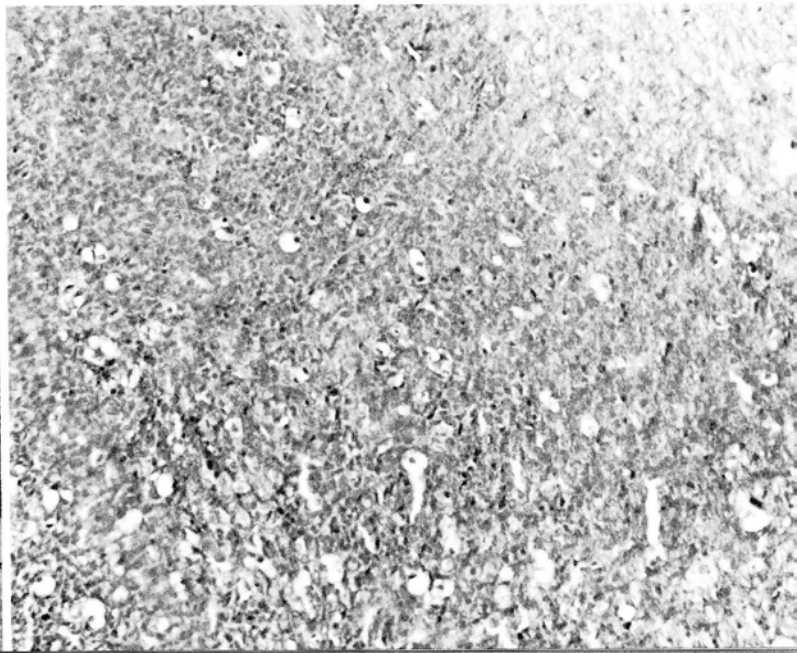


Fig. 4—The "starry sky" pattern is produced by scattered cells with abundant clear cytoplasm. These cells are macrophages. (H & E x 100)



Matthew H. Block, M. D., Denver, Colorado: The accuracy or the specificity of this "starry sky" appearance is really a question of mathematics, because it takes about eighteen to twenty-four hours to clear nuclear debris from a cell that has died; therefore, the number of "starry sky" cells that you see, or the amount of nuclear debris, really depends on how many cells are dying within any period of time and how long it takes to clear the debris. The exact same picture can be reproduced in a small lymphocytic lymphosarcoma by treating the patient with radiations and biopsying the lymph node eight to sixteen hours after irradiation; administration of mustard or cortisone can produce the same type of appearance, provided there are cells that are sensitive to the agent used. There is nothing specific about it; it merely represents cells that are dying and where the nuclear debris has still not been cleared. Obviously, in an individual who has a rather malignant disease where the cells are not spilling into the peripheral blood, we are merely seeing cells dying in the bone marrow as in this particular case.

If the patient had lived long enough, I am quite sure that this patient would eventually have spilled the cells in the peripheral blood and then we would call it leukemia.

Dr. Regato: This patient had blasts in circulation before death.

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15A. *Hodgkin's Disease with Bone Involvement*

Contributed by C. W. Anthony, M. D., D. E. Smith, M. D. and D. C. Dyke, M. D.

Denver, Colorado

THE PATIENT was a 32-year old man in May, 1962, when he gave a history of intermittent precordial pain of 6 years' duration; one year previously he had had hemoptysis and the chest film revealed a "mediastinal tumor" for which he was given nitrogen mustards. On examination there were several small nodes of the neck and axillae. The WBC count was 31,200 per mm^3 and normal differential; the hematocrit 48%.

Dr. Mellins: There is a poorly defined triangular density in the right cardiophrenic angle and extending behind the heart. The right heart border is not effaced. Several linear strands of increased density are seen in the lower third of the right lung field. There is bilateral widening of the superior mediastinal shadow through which several curved densities, indicating enlarged lymph nodes, are seen. The left lung root shows lobulated enlargement representing several large lymph nodes. The intercostal spaces are somewhat uneven in width, in all likelihood as a result of congenital variation. The medial portion of the left 5th rib posteriorly is absent and appears to have been removed surgically. A rounded osteolytic area with poorly defined

Fig. 1—Bilateral hilar enlargement more marked on the left side, betraying the presence of enlarged lymph nodes.

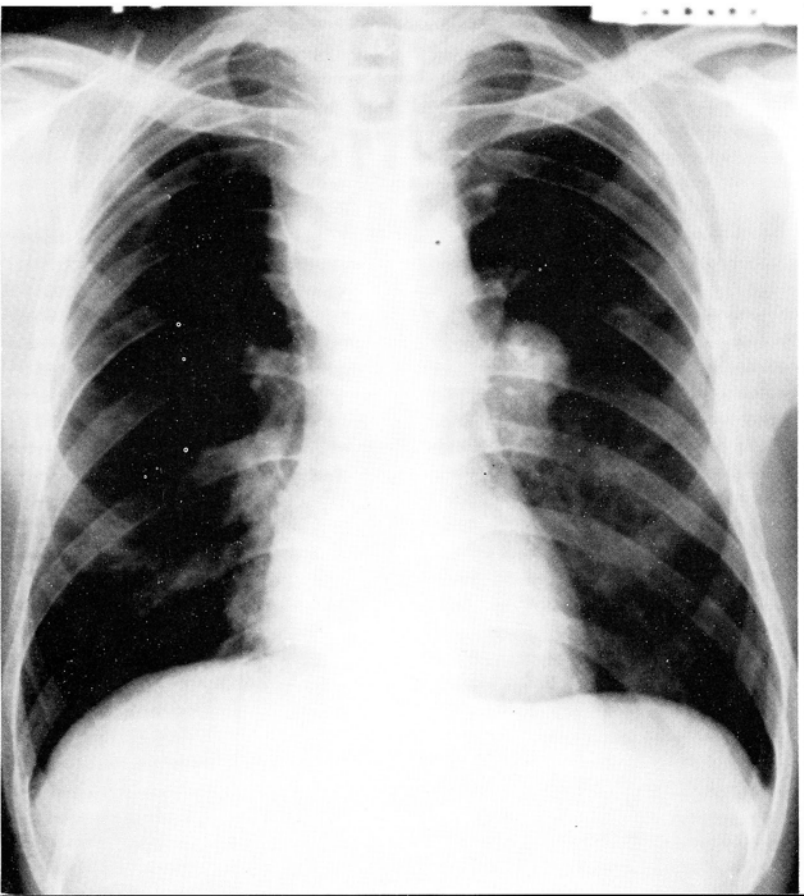
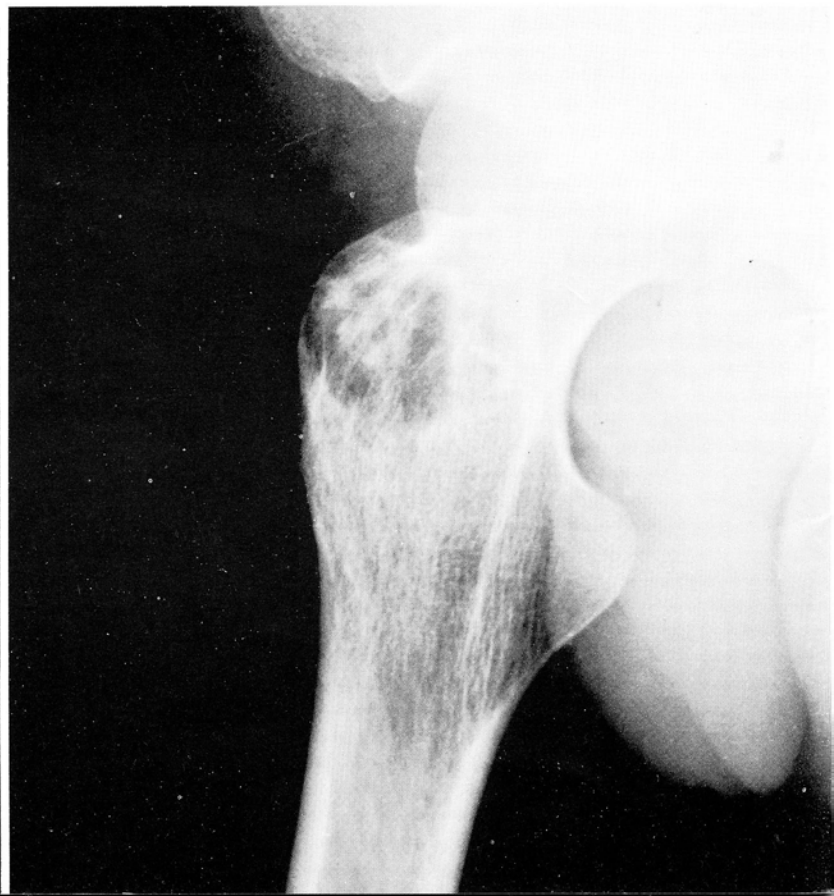


Fig. 2—Osteolytic area of the greater trochanter of the right femur.



margins is seen in the right greater trochanter. Residual bridging trabeculae are noted. Along the lateral aspect of the lesion the cortex is permeated and there is evidence of periosteal reaction of an amorphous type. Multiple small lens-shaped radiolucencies are seen throughout the shaft of the right femur, particularly in its lower third.

The duration of symptoms and the youth of the patient speak against the diagnosis of metastatic carcinoma to the hilar and mediastinal nodes and to the right femur. The lymph node involvement is larger and somewhat more extensive than one usually sees with tuberculous lymphadenitis and the patient is somewhat older. Fungus lesions should be considered but one would except to see parenchymal, rather than a nodal enlargement, in the chest. A lymphomatous lesion would therefore seem the most likely possibility. Hodgkin's disease, when it involves the long bones, most commonly involves the proximal portions of the humerus or femur. It is an osteolytic process in which there are residual or bridging trabeculae. One would like to see a more symmetrical pattern of lymph node involvement in the chest but conceivably this has been altered by therapy.

Dr. Mellins' impression: HODGKIN'S DISEASE.

Roentgenologic Impressions Submitted by Mail

Reticulum-cell sarcoma	41
Hodgkin's disease	25
Bronchial carcinoma	24
Leukemia	17
Others	23

Dr. Mellins: Reticulum-cell sarcoma usually gives a more complete destructive area than in this case and the bridging trabeculae are generally not present in reticulum-cell sarcoma. Bronchial carcinoma with metastasis to bone is a possibility. There is no evidence, however, of peripheral lung lesion, and again I do like the presence of bridging trabeculae in Hodgkin's. I have no support for a diagnosis of leukemia.

Dr. Regato: Dr. J. W. Travis, of Topeka, and Dr. J. T. McClintock, of Denver, also made a diagnosis of Hodgkin's disease; Dr. Neal Goodman and Dr. J. C. Lemon, of Denver, preferred reticulum-cell sarcoma.

Apologia: This clinical and radiographic discussion should now have been followed by a histopathologic evidence of a clear case of Hodgkin's disease which came to autopsy. However, for the first time in about 270 cases studied in these Cancer Seminars, we suffered a mistake in the identification of paraffin blocks in our laboratories: the slides which were distributed to the participants in this Cancer Seminar correspond to another case, originally chosen to be presented, but which we eliminated due to our inability to find the corresponding blocks. The only damage done is that of an erroneous history given to the pathologists; it is questionable that it might have influenced unduly their morphologic interpretation. The history of the patient corresponding to the distributed slides follows:

15B. *Malignant Lymphoma (Lymphocytic Type) of the Small Intestine with Dysproteinemia*

Contributed by R. F. Dillon, M. D., D. L. Dawson, M. D. and J. Karabin, M. D.

Colorado Springs, Colorado

THE PATIENT was a 71-year old man in November, 1960, when he complained of severe right abdominal pain and bleeding. Radiologic examination revealed small bowel obstruction. At exploratory laparotomy a gastrostomy was done and three segments of the small bowel, apparently affected by a tumor, were removed.

Dr. Rappaport: This is one of the best cases of the Seminar and it illustrates Dr. del Regato's skill in transforming a liability into an asset. At low magnification, one sees a massive cellular infiltration of the intestine. The infiltrating cells have obliterated the mucosa and submucosa almost completely. The muscularis mucosa is preserved in some areas, extensively infiltrated in others. The mesenteric fat tissue is heavily infiltrated by proliferating cells.

At high magnification you can see how extensively the *membrana propria* of the mucosa is infiltrated, resulting in wide separation of the intestinal glands. The predominating cells of this neoplasm seem to be differentiated lymphocytes (Fig. 1). However, as you look very carefully, you see many areas in which these lymphocytes have plasmacytoid features (Fig. 2). It is difficult to argue with those who call these cells plasma cells. However, I prefer to regard them as plasmacytoid lymphocytes. For a long time the significance of these cells has not been readily appreciated. However, when a well differentiated lymphocytic lymphoma is not associated with peripheral blood findings of chronic lymphocytic leukemia and when some or many of the tumor cells resemble plasma cells, one should think of a lymphocytic malignancy that is associated with a dysproteinemia, particularly macroglobulinemia (Rappaport). In such instances, periodic-acid-Schiff (PAS) positive staining of the cytoplasm of some of the plasmacytoid lymphocytes is evident. The blood plasma within blood vessels stains intensely with the PAS reagent, indicating the probability that immune globulins rich in hexose are present in the blood. We know that both IgA (gamma A) and IgM (gamma M) are rich in hexose while IgG (gamma G) is not. We also know that IgA is one of the immunoglobulins that are elaborated in multiple myeloma, while IgM is characteristic of macroglobulinemia of Waldenström, which is a lymphoproliferative disease.

Since I interpret this as a lymphocytic, rather than as plasmacytic, malignant tumor, I would like to show you some slides from proven cases of macroglobulinemia from my collection. Note the massive infiltration of the pericapsular tissue with lymphocytes and the intense PAS-positive staining of the plasma in the blood vessels. Hemosiderin-laden macrophages are abundant. This suggests auto-immune hemolytic anemia which is often associated with macroglobulinemia.

At high magnification, the predominating cells are recognizable as lymphocytes. The portal fields of the liver are infiltrated as in chronic lymphocytic leukemia. However, the disease is only very rarely associated with a leu-

Matthew H. Block, M. D., Denver, Colorado: The accuracy or the specificity of this "starry sky" appearance is really a question of mathematics, because it takes about eighteen to twenty-four hours to clear nuclear debris from a cell that has died; therefore, the number of "starry sky" cells that you see, or the amount of nuclear debris, really depends on how many cells are dying within any period of time and how long it takes to clear the debris. The exact same picture can be reproduced in a small lymphocytic lymphosarcoma by treating the patient with radiations and biopsying the lymph node eight to sixteen hours after irradiation; administration of mustard or cortisone can produce the same type of appearance, provided there are cells that are sensitive to the agent used. There is nothing specific about it; it merely represents cells that are dying and where the nuclear debris has still not been cleared. Obviously, in an individual who has a rather malignant disease where the cells are not spilling into the peripheral blood, we are merely seeing cells dying in the bone marrow as in this particular case.

If the patient had lived long enough, I am quite sure that this patient would eventually have spilled the cells in the peripheral blood and then we would call it leukemia.

Dr. Regato: This patient had blasts in circulation before death.

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15A. *Hodgkin's Disease with Bone Involvement*

Contributed by C. W. Anthony, M. D., D. E. Smith, M. D. and D. C. Dyke, M. D.

Denver, Colorado

THE PATIENT was a 32-year old man in May, 1962, when he gave a history of intermittent precordial pain of 6 years' duration; one year previously he had had hemoptysis and the chest film revealed a "mediastinal tumor" for which he was given nitrogen mustards. On examination there were several small nodes of the neck and axillae. The WBC count was 31,200 per mm^3 and normal differential; the hematocrit 48%.

Dr. Mellins: There is a poorly defined triangular density in the right cardiophrenic angle and extending behind the heart. The right heart border is not effaced. Several linear strands of increased density are seen in the lower third of the right lung field. There is bilateral widening of the superior mediastinal shadow through which several curved densities, indicating enlarged lymph nodes, are seen. The left lung root shows lobulated enlargement representing several large lymph nodes. The intercostal spaces are somewhat uneven in width, in all likelihood as a result of congenital variation. The medial portion of the left 5th rib posteriorly is absent and appears to have been removed surgically. A rounded osteolytic area with poorly defined

Fig. 1—Bilateral hilar enlargement more marked on the left side, betraying the presence of enlarged lymph nodes.

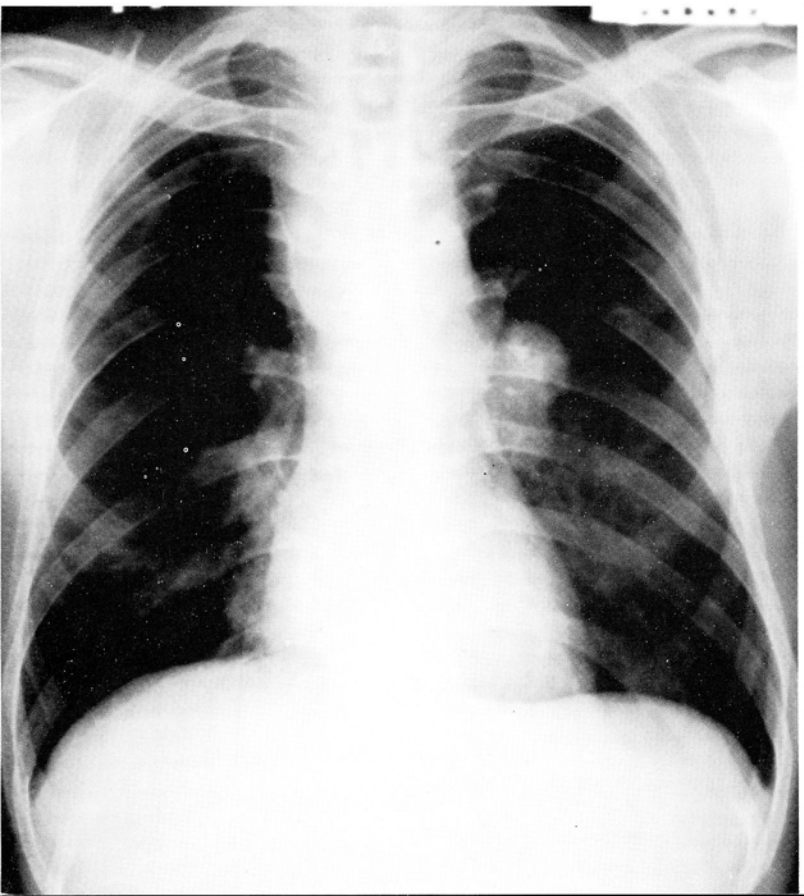
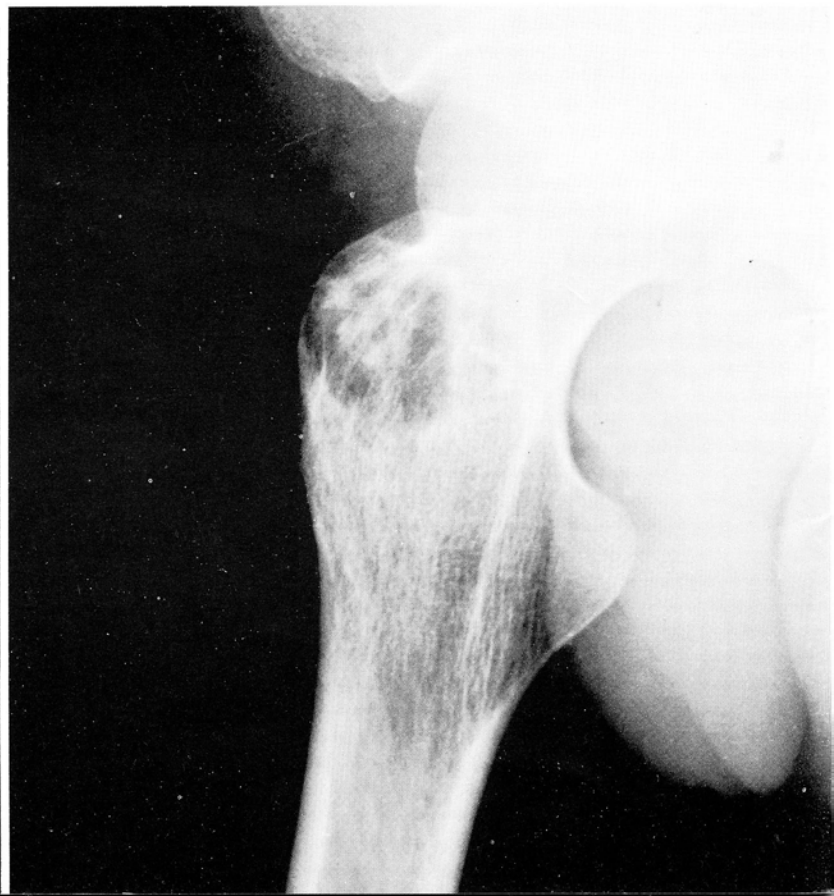


Fig. 2—Osteolytic area of the greater trochanter of the right femur.



margins is seen in the right greater trochanter. Residual bridging trabeculae are noted. Along the lateral aspect of the lesion the cortex is permeated and there is evidence of periosteal reaction of an amorphous type. Multiple small lens-shaped radiolucencies are seen throughout the shaft of the right femur, particularly in its lower third.

The duration of symptoms and the youth of the patient speak against the diagnosis of metastatic carcinoma to the hilar and mediastinal nodes and to the right femur. The lymph node involvement is larger and somewhat more extensive than one usually sees with tuberculous lymphadenitis and the patient is somewhat older. Fungus lesions should be considered but one would except to see parenchymal, rather than a nodal enlargement, in the chest. A lymphomatous lesion would therefore seem the most likely possibility. Hodgkin's disease, when it involves the long bones, most commonly involves the proximal portions of the humerus or femur. It is an osteolytic process in which there are residual or bridging trabeculae. One would like to see a more symmetrical pattern of lymph node involvement in the chest but conceivably this has been altered by therapy.

Dr. Mellins' impression: HODGKIN'S DISEASE.

Roentgenologic Impressions Submitted by Mail

Reticulum-cell sarcoma	41
Hodgkin's disease	25
Bronchial carcinoma	24
Leukemia	17
Others	23

Dr. Mellins: Reticulum-cell sarcoma usually gives a more complete destructive area than in this case and the bridging trabeculae are generally not present in reticulum-cell sarcoma. Bronchial carcinoma with metastasis to bone is a possibility. There is no evidence, however, of peripheral lung lesion, and again I do like the presence of bridging trabeculae in Hodgkin's. I have no support for a diagnosis of leukemia.

Dr. Regato: Dr. J. W. Travis, of Topeka, and Dr. J. T. McClintock, of Denver, also made a diagnosis of Hodgkin's disease; Dr. Neal Goodman and Dr. J. C. Lemon, of Denver, preferred reticulum-cell sarcoma.

Apologia: This clinical and radiographic discussion should now have been followed by a histopathologic evidence of a clear case of Hodgkin's disease which came to autopsy. However, for the first time in about 270 cases studied in these Cancer Seminars, we suffered a mistake in the identification of paraffin blocks in our laboratories: the slides which were distributed to the participants in this Cancer Seminar correspond to another case, originally chosen to be presented, but which we eliminated due to our inability to find the corresponding blocks. The only damage done is that of an erroneous history given to the pathologists; it is questionable that it might have influenced unduly their morphologic interpretation. The history of the patient corresponding to the distributed slides follows:

15B. *Malignant Lymphoma (Lymphocytic Type) of the Small Intestine with Dysproteinemia*

Contributed by R. F. Dillon, M. D., D. L. Dawson, M. D. and J. Karabin, M. D.

Colorado Springs, Colorado

THE PATIENT was a 71-year old man in November, 1960, when he complained of severe right abdominal pain and bleeding. Radiologic examination revealed small bowel obstruction. At exploratory laparotomy a gastrostomy was done and three segments of the small bowel, apparently affected by a tumor, were removed.

Dr. Rappaport: This is one of the best cases of the Seminar and it illustrates Dr. del Regato's skill in transforming a liability into an asset. At low magnification, one sees a massive cellular infiltration of the intestine. The infiltrating cells have obliterated the mucosa and submucosa almost completely. The muscularis mucosa is preserved in some areas, extensively infiltrated in others. The mesenteric fat tissue is heavily infiltrated by proliferating cells.

At high magnification you can see how extensively the *membrana propria* of the mucosa is infiltrated, resulting in wide separation of the intestinal glands. The predominating cells of this neoplasm seem to be differentiated lymphocytes (Fig. 1). However, as you look very carefully, you see many areas in which these lymphocytes have plasmacytoid features (Fig. 2). It is difficult to argue with those who call these cells plasma cells. However, I prefer to regard them as plasmacytoid lymphocytes. For a long time the significance of these cells has not been readily appreciated. However, when a well differentiated lymphocytic lymphoma is not associated with peripheral blood findings of chronic lymphocytic leukemia and when some or many of the tumor cells resemble plasma cells, one should think of a lymphocytic malignancy that is associated with a dysproteinemia, particularly macroglobulinemia (Rappaport). In such instances, periodic-acid-Schiff (PAS) positive staining of the cytoplasm of some of the plasmacytoid lymphocytes is evident. The blood plasma within blood vessels stains intensely with the PAS reagent, indicating the probability that immune globulins rich in hexose are present in the blood. We know that both IgA (gamma A) and IgM (gamma M) are rich in hexose while IgG (gamma G) is not. We also know that IgA is one of the immunoglobulins that are elaborated in multiple myeloma, while IgM is characteristic of macroglobulinemia of Waldenström, which is a lymphoproliferative disease.

Since I interpret this as a lymphocytic, rather than as plasmacytic, malignant tumor, I would like to show you some slides from proven cases of macroglobulinemia from my collection. Note the massive infiltration of the pericapsular tissue with lymphocytes and the intense PAS-positive staining of the plasma in the blood vessels. Hemosiderin-laden macrophages are abundant. This suggests auto-immune hemolytic anemia which is often associated with macroglobulinemia.

At high magnification, the predominating cells are recognizable as lymphocytes. The portal fields of the liver are infiltrated as in chronic lymphocytic leukemia. However, the disease is only very rarely associated with a leu-

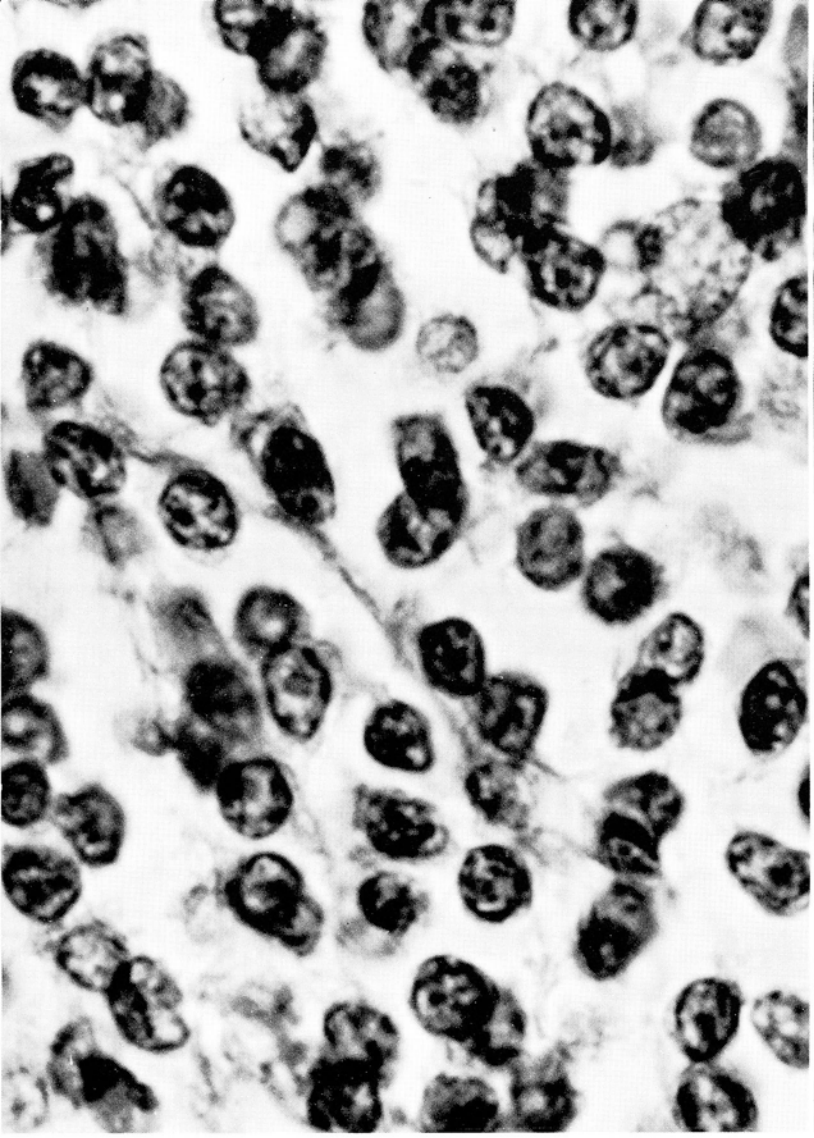


Fig. 1—The tumor is composed of well differentiated mature appearing lymphocytes. There is little variation in nuclear size and shape. In this field none of the lymphocytes have plasmacytoid features. (H & E x 1000)

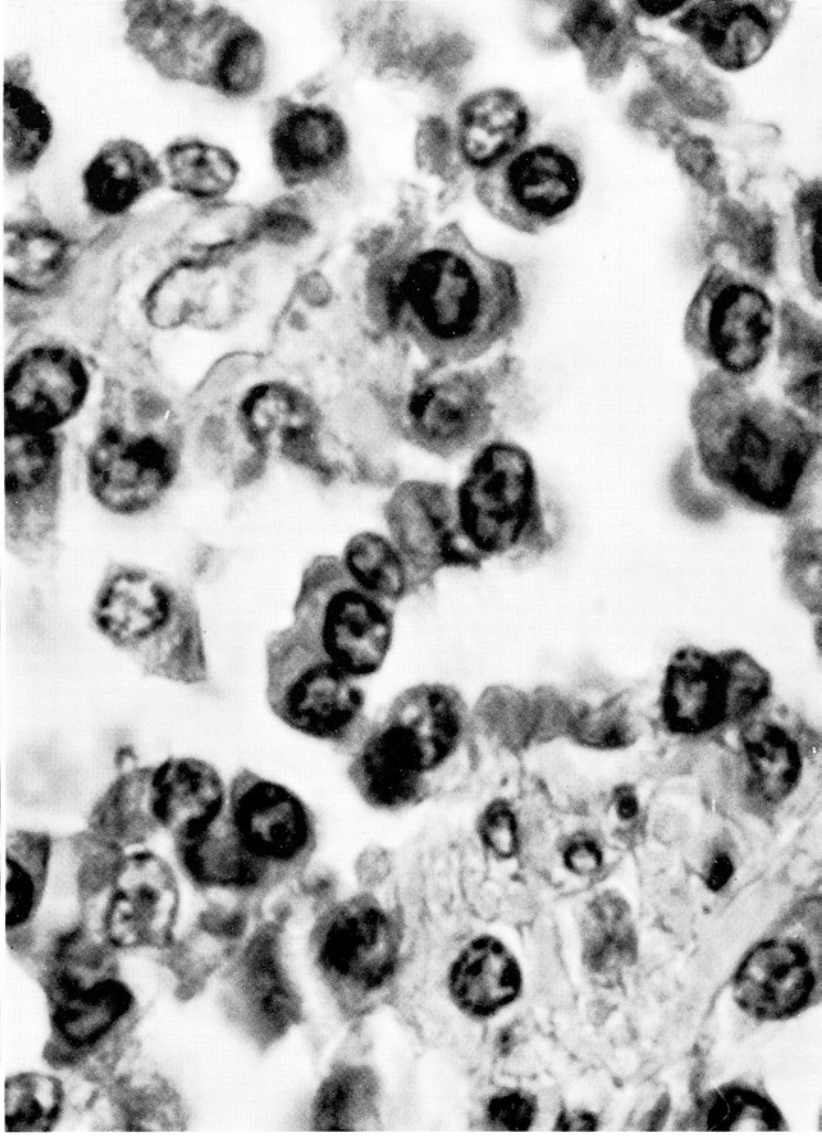


Fig. 2—Most of the cells have nuclei that are similar to those shown in Fig. 1. However, many of the lymphocytes have a fairly abundant amount of deep staining cytoplasm and eccentrically situated nuclei. These cells are interpreted as plasmacytoid lymphocytes and are characteristic of macroglobulinemia. (H & E x 1000)

kemic blood picture (Rappaport). Some of the lymphocytes are plasmacytoid. Some contain PAS-positive material in the cytoplasm. In other instances, many of the lymphocytes have plasmacytoid features and their cytoplasm varies from faintly to strongly PAS-positive. Here you see the characteristic finding of intranuclear PAS-positive material as described by Dutcher and Fahey in their excellent paper on the histopathology of macroglobulinemia.

It has been shown subsequently that these intranuclear PAS-positive inclusions may be evident not only in macroglobulinemia but also in IgA myelomas and that similar inclusions, although PAS-negative, may occur in IgG myelomas (Brittin, Tanaka and Brecher). These intranuclear inclusions show a specific immuno-fluorescence with either anti-gamma M or anti-gamma A or anti-gamma G rabbit serum (Dutcher and Fahey).

In this bone marrow smear from a patient with macroglobulinemia many of the cells are readily recognizable as lymphocytes. The plasmacytoid cells among them have the nuclear features of lymphocytes, while the cytoplasm stains like that of plasma cells. Azure granules are evident in some of the cells.

Based upon the histologic features of this tumor, my diagnosis was "malignant lymphoma, lymphocytic type, with plasmacytoid features consistent with dysproteinemia".

Dr. Rappaport's diagnosis: MALIGNANT LYMPHOMA, lymphocytic type, with plasmacytoid features, consistent with dysproteinemia.

Histopathologic Diagnoses Submitted by Mail

Lymphosarcoma (lymphocytic)	69
Malignant lymphoma	30
Plasmacytoma (myeloma)	38
Reticulum-cell sarcoma	6
*Hodgkin's disease	10
Two others	4

Dr. Rappaport: It appears that the majority of these pathologists were more impressed with the lymphocytic than with the plasmacytoid component of this neoplasm, and called it lymphosarcoma. While a strong minority called it plasmacytoma, this pinpoints the differential diagnostic problem in this and similar cases. I do not believe either reticulum-cell sarcoma or Hodgkin's disease are defensible diagnoses. Malignant lymphoma without further classification or characterization is an insufficient diagnosis in a case of this type.

Dr. Regato: Sister Joseph Ignatius, of Cincinnati, also made a diagnosis of malignant lymphoma, lymphocytic type. Dr. J. Kissane, of St. Louis, and Dr. M. R. Abell, of Ann Arbor, preferred plasmacytoma.

Subsequent history: Following resection, the patient received a short series of treatments with a relatively small dose of radiations administered with conventional roentgentherapy. Five years later, in January, 1965, the patient developed a new intestinal obstruction: an exploratory laparotomy revealed the presence of post-operative adhesions as the cause of the symptoms; the total proteins were 8.9 gm %.

In August, 1965, the patient developed again abdominal pain, distention, nausea and diarrhea. There was no palpable superficial adenopathy, no hepatomegaly, no splenomegaly. The lymphangiogram revealed evidence of enlarged para-aortic lymph nodes. The hemoglobin was 13 gm %; the total proteins were 11.6 gm % with 7.5 gm of globulins; by electrophoresis an abnormal gamma component of 5.6 gm % was noted. A diagnosis of myeloma was entertained; no bone lesions could be identified. The bone marrow was about 40% cellular with pleomorphic, fluted nodules of lymphocytes and plasma cells throughout the specimen; plasma cells were increased within the narrow interstices, without relation to blood vessels.

From November 24th, 1965, to January 26th, 1966, the patient received Cobalt-60 teletherapy through two large fields 15 x 24 cm and 20 x 24 cm, covering the entire abdomen and pelvis. A total dose of approximately 3,300 R was administered to the mid plane of the abdomen in 64 days. The patient's symptoms disappeared during treatment but the protein electrophoresis remained abnormal. The patient was last seen in April, 1967, at which time he had regained weight and was entirely asymptomatic; there were no palpable superficial adenopathy or splenomegaly; the chest film showed no abnormalities.

D. L. Dawson, M. D., Colorado Springs, Colorado: On the original serum protein electrophoresis Dr. Robert Maier, of Penrose Hospital, put a PAS stain directly upon the paper strip and found the strongly staining hexosamine rich component, staining PAS positive on the strip; this was the reason we sent this material for ultra-centrifugation. We have since confirmed the high levels by doing local immunodiffusion studies; they are still present. His serum viscosity is about 3.1 at the present time; he has never had any problems with his elevated serum viscosity.

Dr. Steinfeld: If the macroglobulin level gets very high, these patients do get into trouble with a hyperviscosity syndrome; some of them have actually gone blind. You can treat this with plasmaphoresis by removing the protein from a number of units of blood; that is, remove a unit of blood, spin it down and get back the red cells and follow with therapy. This patient responded to radiotherapy; they respond equally well to very low doses of alkylating agents given over a long period of time. We have a number of patients in whom the macroglobulin has disappeared with therapy which has continued for months.

The prognosis in this malignant form of lymphoma is generally much better than most others, despite the advanced age of most of the patients. The macroglobulin in many instances is a cryomacroglobulin and when the patient gets out in the cold he may suffer symptoms whereas he may not if he stays in a warm climate.

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OUR GUEST SPEAKERS

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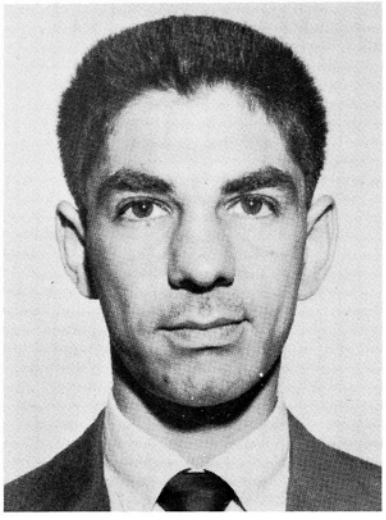

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