Lymphography in the Diagnosis of Maligant Lymphoma

Mutsumasa Takahashi, M.D.

悪性リンパ腺腫に於けるリンパ系造影法の臨床的研究

九州大学医学部放射線医学教室（主任：入江英雄教授）
スタンフォード大学医学部放射線医学教室（主任：Herbert L. Abrams教授）
高　橋　睦　正

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リンパ系造影法を206例の悪性リンパ腺腫の診断に用い，1年以上の経過観察を行い，次の様な結果を得た．

1．悪性リンパ腺腫の診断能は80.6％である．リンパ肉腫，及び細網肉腫はホジキン氏病及び巨濾胞性リンパ腫より診断が容易である．

2．30例の“false negative”のうち大多数のホジキン氏病は，6カ月以後，12カ月以内に異常な後腹膜リンパ腺腫の発生をみたが，細網肉腫及びリンパ肉腫の異常リンパ腺出現は6カ月以内にみられた．

3．全症例を考慮に入れると，ホジキン氏病及び巨濾胞性リンパ腫の“false negative”の頻度は，細網肉腫及びリンパ肉腫の“false negative”の頻度より高い．

4．“foamy appearance”及び陰影欠損像の程度分類は確定診断をする上に有益である．

5．リンパ管が24時間後にもみられる場合は，他の変化がなくても異常の場合が多い．

6．リンパ系造影法でリンパ腺腫の組織像を推察することは，ある程度可能であるが，臨床的な意味はあまりない．

7．リンパ系造影診断の確定しない例には，著者が考案した測定値が有用である．

測定値A：正常 3.0cm以内
　　A：脊椎前面と淋巴腺の距離
測定値B：正常 2.0cm以内
　　B：脊椎右縁と淋巴腺の距離
測定値C：正常 2.0cm以内
　　C：脊椎左縁と淋巴腺の距離
リンパ腺の大きさ：正常直径 2.5cm以内

8．下大静脈造影法はリンパ系造影読影上，補助的価値がある．7例は，リンパ系造影が正常にもかかわらず，下大静脈造影は異常であつた．

9．重症な副作用は，既存の肺疾患がある場合及び大量の造影剤使用後にみられる場合が多い．

Introduction

Lymphography has been widely applied to the study of malignancy in recent years (1, 8, 14, 26, 35, 43). Application to the diagnosis and management of malignant lymphoma (4, 21, 24, 36) as well as lymphedema (20, 23) has been the most fruitful aspect of this method. However, there remains some skepticism toward this method as the accumulated experience indicates that lymphography has considerable technical difficulties, inherent complications, and somewhat poor diagnostic accuracy (2, 6, 7, 11, 13, 15, 19, 29, 30, 33, 40, 41). It also demands great skill and experience in interpretation. Our

From the Department of Radiology, Kyushu University School of Medicine, Fukuoka, Japan, and Department of Radiology, Stanford University School of Medicine, Palo Alto, California, U.S.A.

experience has been that the most difficult aspect of this method lies in the interpretation. Other problems can be surmounted to certain extent. The purpose of this communication is to report the author's experience of lymphography in the diagnosis of malignant lymphoma with special emphasis on diagnostic accuracy, analysis of false negative cases, correlation of lymphographic and histologic findings and some measurements which have been helpful in the evaluation of borderline lymphograms. The role of inferior vena cavography and complications of lymphography are also discussed.

Technique

The technique employed is a modification of the method originally reported by Kinmonth et al. (1, 23). Light sedation with 100 mg. Seconal is routinely used for adults, but heavy sedation or general anesthesia is necessary for children under 5 years of age.

The examination is performed on a radiographic table equipped with an image intensifier and a television circuit. The patient reclines comfortably on the table with the knees bent and the sole of the feet flat on the table. Surgical preparation is performed to both feet.

One cc. of equal parts of Evans blue and procaine hydrochloride is injected intradermally and subcutaneously into the first and second interdigital spaces bilaterally. Approximately 10 minutes later a transverse cutdown is carried out on the dorsum of each foot over the first and second metatarsals. A lymphatic vessel is carefully isolated and cannulated with a 28 or 30 gauge needle attached to a No. 10 polyethylene catheter. A tight 5-0 silk ligature is placed over the needle. At first a small amount of saline with several air bubbles is injected to identify a leakage at the needle tip. If there is no leakage, the needle and the polyethylene catheter are secured by means of sterile adhesive tapes. Ethiodol injection in a 10 cc. syringe is started by means of a weight injector on which 10 to 20 lb. weights can be applied. After 4 to 5 cc. of Ethiodol is injected, flow of contrast material is observed intermittently under fluoroscopic control. When the cisterna chyli is visualized, or obstruction to the lymphatics is observed, the injection is discontinued. Usually 7 to 8 cc. of Ethiodol is injected over a period of 45 minutes. When the cisterna chyli is not visualized, whole 10 cc. of Ethiodol is injected.

Roentgenograms are obtained immediately after the completion of the injection and repeated in 24 hours. Routine filming includes anteroposterior and both oblique views of the pelvis, anteroposterior, lateral and both oblique views of the abdomen and anteroposterior and lateral views of the chest with Bucky technique. Laminograms are frequently used when suspicious nodes are identified.

In order to supplement lymphography, inferior vena cavography (1) is performed on most of the patients 24 to 48 hours after a lymphographic procedure. No. 205 polyethylene catheters are inserted into both femoral veins by a modified Seldinger technique and advanced into the external iliac veins. Forty cc. of Renografin 60 is injected through a Y-shaped connector during relaxed expiration at a pressure of 100 lbs. on a Cordis pressure injector. Three separate injections were made with a single filming in the anteroposterior, right posterior oblique and right cross-table lateral projections.

Contraindications to lymphography are related to poor local wound healing, sensitivity to contrast agent and decreased pulmonary function (2). Thus, lymphograms are not performed in patients with marked edema, bleeding tendency, dermatitis or local infection. The study is also contraindicated when there is a previous history of sensitivity to iodine. Chest films are always obtained to rule out pulmonary lesions such as moderate to extensive pulmonary emphysema, atelectasis involving more

than one lobe and large infiltrating lesions. Patients with the above pulmonary lesions are prone to develop severe pulmonary complications (2, 40).

Clinical Material

Two hundred and six lymphograms on patients with histologically proven malignant lymphoma at Stanford Medical Center were reviewed. At least one year's follow-up was available on all patients. There was significant varia tion in age and sex (Table I).

The cases were subdivided into the following groups according to the initial interpretation, the results of one or more year's follow-up and histologic types (Table II).

Table 1. Age Distribution of 206 Patients with Biopsy Proven Lymphoma

Age In Years	Hodgkin's Disease	Lympho-Sarcoma	Reticulum Cell Sarcoma	Giant Follicular Lymphoma
0–10	4	0	2	0
11–20	26	4	2	1
21–30	33	3	1	0
31–40	30	4	4	2
41–50	14	12	17	4
51–60	6	5	13	4
61–70	4	3	4	1
71–80	1	0	2	0
80+	0	0	0	0
	118	31	45	12
Total	206 Patients			

Table II. Results of Lymphography in Different Types of Lymphoma

	Total Number Patients	Positive	Negative	False Positive	False Negative	Diagnostic Accuracy
Hodgkin's Disease	118	41	52	6	19	78.8%
Lymphosarcoma	31	16	11	1	3	87.1%
Reticulum Cell Sarcoma	45	23	14	2	6	82.1%
Giant Follicular Lymphoma	12	5	4	1	2	75.0%
Total	206	85	81	10	30	80.6%

Group I—Positive. Eight-five patients were included in this group. Cases were considered positive if the initial positive interpretation was subsequently confirmed. Initial criteria of abnormality included a foamy appearance of the nodes, irregular lymph node margings and filling defects with replacement of at least 25% of the node. A size larger than 2.5 cm. was considered abnormal. In all cases there were alterations of the internal architecture and/or enlargement of the lymph nodes. Histologic verification of the positive diagnosis was obtained in many of the early cases. Subsequently, proof of the correctness of the initial interpretations was frequently based on the alterations in architecture and size following radiotherapy or chemotherapy. The architecture of the involved nodes usually reverted to normal by the end of treatment. The change in size and appearance of the involved nodes following therapy was dramatic, and was clearly distiguishable from the gradual, slight decrease in size observable in normal, non-

irradiated nodes following lymphography (9, 39). In a small number of cases there was no change in the "positive" lymphogram following therapy; these cases were excluded from the study since the initial "positive" interpretation could not be verified.

Group II—Negative. This group comprises 81 patients. The lymphogram was considered negative when all nodes were within the normal range of size, less than 2.5 cm. in length, and showed a coarsely granular or homogeneously dense appearance with intact sharp margins (6, 18). A few cases were also diagnosed as normal when a single node was larger than 2.5 cm., but the architecture of all nodes was normal. All patients in this category had at least one year's follow-up without evidence of retroperitoneal node involvement or change in the size and appearance of the nodes. The presence of multiple small filling defects, usually in smaller nodes, did not preclude a negative diagnosis. When larger nodes possessed multiple filling defects, the diagnosis was considerably more difficult. Patients who received prophylactic radiation therapy to retroperitoneal nodes were excluded from this study.

Group III—False Positive. There were 10 cases in this group. False positive cases were those originally interpreted as positive, but without clinical evidence of retroperitoneal disease or significant change in architecture and size of the nodes detected during a one year follow-up period. These patients did not receive therapy. Most of these cases had one or two nodes which were larger than 2.5 cm. in length or contained large filling defects (Fig. 1). These were considered in retrospect to be nonspecific inflammatory changes. Minimal foaminess of nodes also presented difficulty in interpretation. In one of these cases did the subsequent clinical course indicate retroperitoneal node involvement.

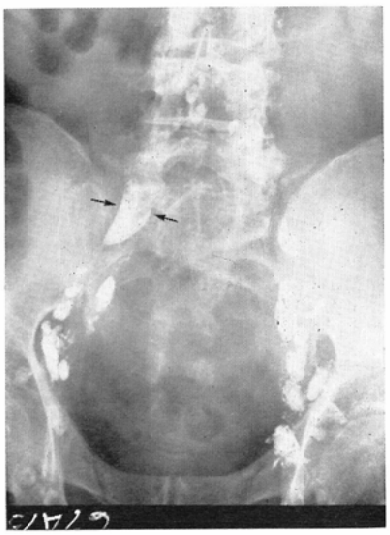
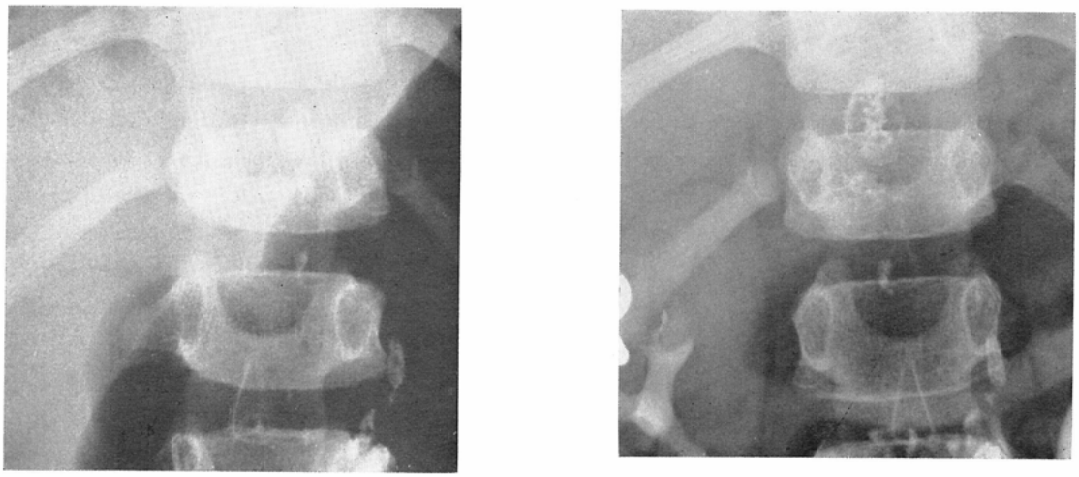


Fig. 1 False positive. A large filling defect in a slightly enlarged node (2 arrows). Second examination 2 years later showed no change in the appearance of this lymph node.

Group IV—False Negative. False negative cases were those considered negative at lymphography, with development of retroperitoneal node involvement within the first year of follow-up. These cases have been categorized on the assumption that the clear-cut development of involvement within 12 months indicated the presence of disease in the nodes at the time of the lymphogram. This is, then, a liberal inter-

pretation of "false negatives", based on the concept that disease in the primary area of involvement can be eliminated by radical radiotherapy and that the subsequent appearance of grossly positive nodes implied that disease was present at the time of the initial examination (22).

Thirty cases were considered false negatives. Four had exploratory laparotomy after lymphography. Including these four, there was a total of 11 out of the 30 false negative cases in which retrospective diagnosis was at variance with the initial interpretation. In 9 of these, there was significant foaminess of the nodes; in 6, enlargement of the nodes; in 3, significant filling defects; and in 1, abnormal position of the nodes. One-third of the group of false negatives, therefore, could be considered interpretive errors rather than deficiences of the method. There were 9 cases which could not be considered "positive" or "equivocal" by our present criteria (Fig. 2). In the remaining 10 patients, minimal findings were present, insufficient to make a positive diagnosis even in retrospect. Among the minimal findings were foamy appearance of the node in 7 patients, nodes larger than 2.5 cm. in length in 4, filling defects or marginal irregularity in 2, and abnormal position of the nodes in 3.



(A) (B)

Fig. 2 Hodgkin's disease. False negative.

A. Initial lymphogram (5-6-65) demonstrates normal para-aortic nodes. At the level of the T11-T12 intervertebral space a node is visualized which is normal in size and appearance. All other nodes were entirely normal.

B. Second lymphogram (2-16-66) shows definite enlargement of the node at the T11-T12 interspace with multiple filling defects. In addition there is a node overlying the 12th thoracic vertebral body, poorly visualized, which was also somewhat enlarged and had filling defects. All other nodes were normal. Although review of the initial lymphogram demonstrated no evidence of disease, this patient was classed as a "false negative" because of the appearance of retroperitoneal node involvement eight months after he was first seen.

Of the 30 false negative cases, 19 were cases of Hodgkin's disease, 6 of reticulum cell sarcoma, 3 of lymphosarcoma, and 2 of giant follicular lymphoma. When the number of cases in each histologic type was considered, there was a tendency for Hodgkin's disease to present more difficulty in interpretation

than the other histologic types, but the number was not sufficient to draw definitive conclusions. Furthermore, the patients with Hodgkin's disease (14 cases) generally developed roentgenographically demonstrable abnormalities on follow-up films between 6 and 12 months, whereas those with reticulum cell sarcoma (4 cases) and lymphosarcoma (3 cases) revealed distinctive changes within 6 months following lymphography. Exceptions to this observation were 2 patients with Hodgkin's disease in whom enlargement of the nodes was noted in 2 months. There were also 5 additional patients with Hodgkin's disease in whom abnormal retroperitoneal nodes appeared after one year. These 5 cases were not included under "false negative".

Lymphographic Pattern

Lymphographic findings of malignant lymphoma are numerous (1, 8, 38, 43), but can be summarized in four major patterns: (1) foamy appearance of the lymph nodes, (2) filling defects or marginal irregularity of the nodes, (3) enlargement of the lymph nodes, and (4) abnormal lymphatics. One or more patterns are present in each case. These patterns are all due to a primary change in the nodes involved by lymphoma.

1. *Appearance of the Lymph Nodes.* Interpretation of internal architecture at lymphography is frequently subjective, varying widely depending on a radiologist's previous experience. If standard criteria for the foamy appearance and filling defects could be established, then the interpretation would be made on a more objective ground and less experienced radiologists might improve their diagnostic accuracy. An attempt was made to correlate the degree of foamy appearance and filling defects with the diagnoses.

Five experienced radiologists reviewed 90 lymphograms which consisted of 30 arbitrarily selected cases each from Group I (Positive), Group II (Negative), and Group IV (False Negative), and recorded their grading on foaminess and filling defects in the nodes (Table III). A node was selected beforehand in each case on the 24-hour lymphogram as the most representative or abnormal of the node group. Difference in interpretation among five radiologists was reconciled by accepting the opinion of the majority of the group.

Table III. Foaminess and Filling Defects of Nodes in Lymphoma

	Total	Grade 0	Grade I	Grade II	Grade III
Foaminess					
Group I (positive)	30	2	5	10	13
Group II (negative)	30	19	10	1	0
Group IV (false negative)	30	7	19	4	0
Filling Defects					
Group I (positive)	30	3	10	11	6
Group II (negative)	30	13	16	1	0
Group IV (false negative)	30	6	21	3	0

A. *Foamy Appearance:* Degree of foamy appearance was classified as Grade 0 (normal), Grade I (slight), Grade II (moderate), and Grade III (markedly foamy and reticular). Representative film were used as standards (Fig. 3).

The nodes in negative cases (Group II) usually showed foaminess, classified as Grade 0 and Grade I. It is noteworthy that the normal nodes reveal a slightly foamy appearance. Most of the positive cases (Group I) revealed Grade II and III foaminess, while a small number of cases in this group are classified

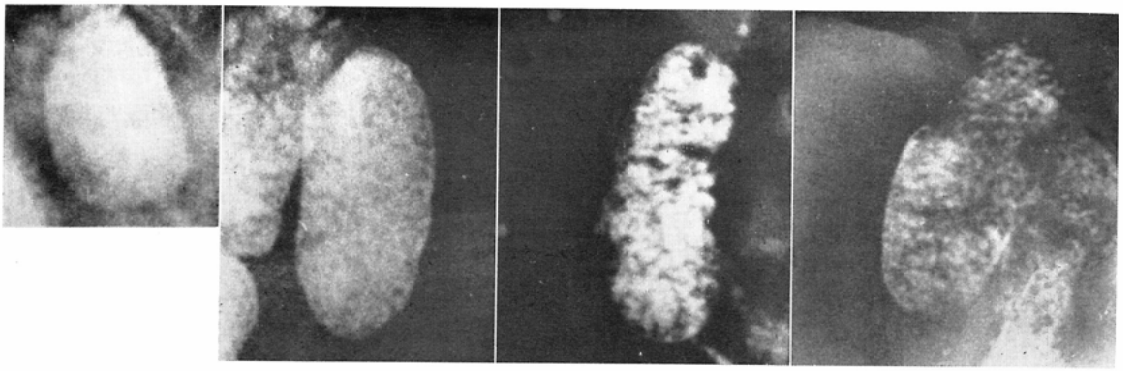


Fig. 3. Standard roentgenograms for foamy appearance. From left to right: Grade 0 (normal), Grade I (slight), Grade II (moderate), and Grade III (marked).

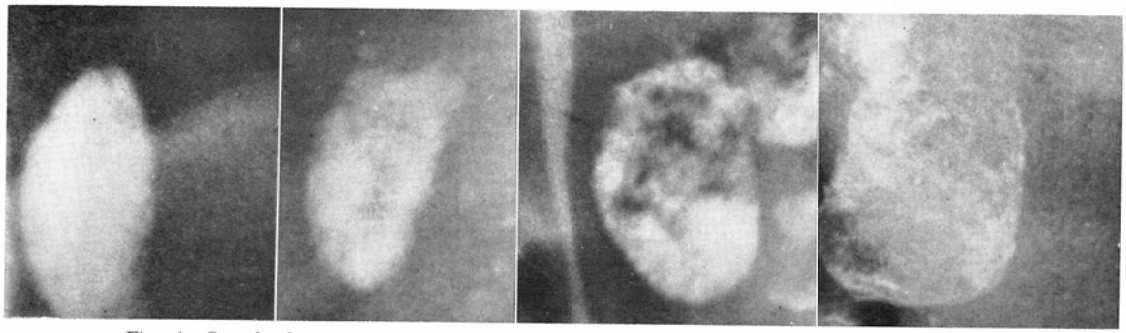


Fig. 4 Standard rontgenograms for filling defects. From left to right: Grade 0 (no filling defects), Grade I (less than 1/3), Grade II (1/3 to 2/3), and Grade III (more than 2/3).

as Grade 0 or Grade I.

Foamy appearance of the nodes was one of the most important criteria in evaluation of lymphomas. When the nodes show Grade I foaminess, the cases should be evaluated with extreme caution utilizing other criteria for definitive diagnosis. Grade II and Grade III foaminess was always indicative of malignant lymphoma with an exception of one case whose foamy node (Grade II) did not change over a year.

B. *Filling Defects:* Evaluation of filling defects was also performed on a similar classification as foamy appearance (Fig. 4).

Grade 0 (no filling defect)

Grade I (less than 1/3 of a node in question)

Grade II (filling defect between 1/3 and 2/3 of a node)

Grade III (more than 2/3, including a "rim sign")

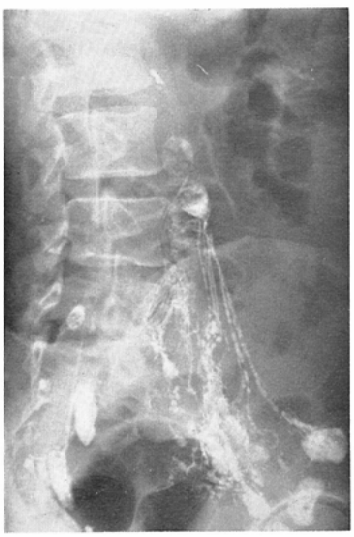
Standard roentgenograms were also utilized for the evaluation.

All 30 cases except one in Group II contained no filling defects or small filling defects (Grade 0 and Grade I). Of 30 abnormal cases, 17 showed moderate to extensive replacement of lymph nodes by lymphoma while 13 cases failed to reveal any significant filling defects. When a "rim sign" was present, the node always proved to be abnormal.

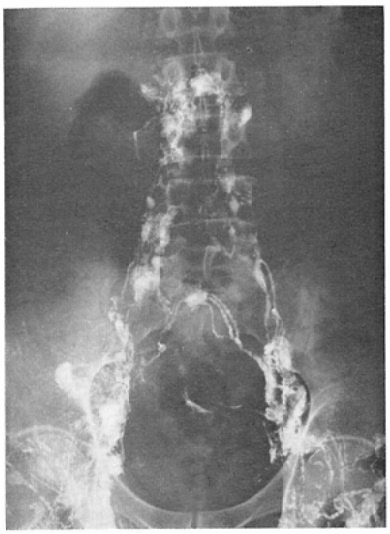
Grading as described in this study seems to help to separate normal nodes from abnomal nodes, although wide variation was seen in the abnormal group.

False negative cases in Group IV were discussed in the previous section.

2. *The Lymphatic Channels.* Persistence of multiple channels on the 24-hour films were usually indicative of obstructive process in the lymph nodes due to malignant lymphoma (Fig. 5 A & B), as was



(A)



(B)

Fig. 5. Persistent filling of the lymphatics on 24-hour films.

A. Hodgkin's disease. There are large filling defects in the nodes at the level of L3-4. Multiple channels remain densely filled with contrast agent, extending from the inguinal and iliac nodes to the para-aortic nodes.

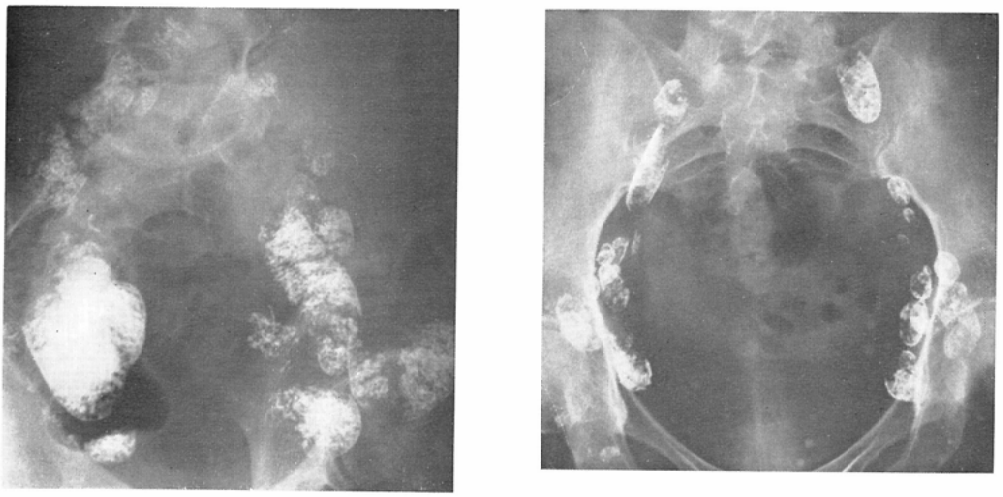
B. Reticulum cell sarcoma. There are multiple nodes which are slightly enlarged, foamy, and contain filling defects. Collateral lymphatic flow is noted via perivesical and right retroperitoneal lymphatics. Common iliac and presacral channels remain densely opacified at 24 hours.

displacement of the lymphatic channels on the initial films (1). Moderate persistent filling of channels was observed in 4 of 30 false negative lymphograms, but only 3 cases showed similar persistent filling among 86 negative studies. Extensive persistent visualization was usually seen in patients with positive lymphograms, but other lymphographic findings were most apparent in these cases. Although the author has not encountered cases in which marked channel filling is the only finding, the author feels that moderate filling on 24-hour films direct his attention to a possible abnormal lymphogram.

3. *Correlation of Lymphographic and Histologic Diagnosis.* More specific differentiation of the histologic types of lymphoma was attempted, utilizing positive lymphograms (Table IV). Lymphosarcoma and reticulum cell sarcoma typically produced a granular or reticular background pattern in a moderately to extensively enlarged node (8,45) (Fig. 6 A). A linear filling of the marginal sinus was frequently seen (Fig. 6 B), although a portion of the sinus was occasionally destroyed when a node was markedly enlarged (45). In a small number of cases, almost all internal architecture was replaced by neoplasm and only

Table IV. Differentiation of Types of Lymphoma by Lymphographic Pattern

	Total	Correct	Indeterminate	Incorrect
Reticulum Cell Sarcoma	23	10	7	6
Lymphosarcoma	16	8	5	3
Hodgkin's Disease	41	20	16	5
Giant Follicular Lymphoma	5	3	1	1
Total	85	41	29	15



(A) (B)

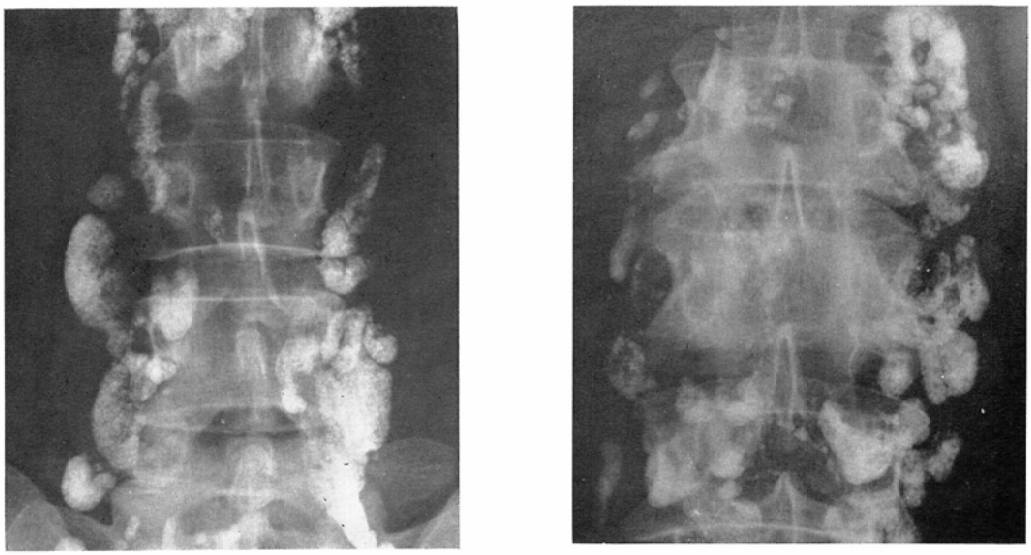
Fig. 6. Characteristic appearance of lymphosarcoma and reticulum cell sarcoma.

A. Lymphosarcoma. There is extensive enlargement of all visualized nodes with foamy and reticular appearance. Subcapsular filling is apparent. Non-filling of multiple para-aortic nodes was noted.

B. Reticulum cell sarcoma. Subcapsular sinuses are well demonstrated. Some nodes have a classical foamy appearance, while others contain filling defects.

a marginal sinus was demonstrated on lymphograms. It was not possible to separate these two histologic entities by lymphography. Hodgkin's disease had a tendency to show one of the following lymphographic patterns: (1) a slightly to moderately foamy appearance in slightly enlarged nodes in almost all node-bearing areas (Fig. 7 A); (2) minimally enlarged or normal sized nodes with slight to moderate filling defects, usually in entire para-aortic and common iliac regions; and (3) localized involvement of a few nodes in the para-aortic or common iliac regions (Fig. 7 B). Giant follicular lymphoma could not be separated from Hodgkin's disease with an exception of one case which showed extensively enlarged, foamy nodes in the external iliac and inguinal nodes without involvement of para-aortic nodes (Fig. 8). This type of lymphographic pattern is said to be frequently related to giant follicular lymphoma (8).

The above criteria were applied to all 85 positive lymphograms (Table IV). No attempt was made to separate reticulum cell sarcoma from lymphosarcoma or giant follicular lymphoma from Hodgkin's disease. In 41 of 85 positive studies the correct diagnoses were made. An incorrect suggestion of histologic type was made in 15. In 29 of 85 positive lymphograms, findings did not permit the histologic differentiation of the type of lymphoma.



(A) (B)

Fig. 7. Lymphographic appearance of Hodgkin's disease.

A. There is a foamy appearance in slightly enlarged nodes seen in almost all node-bearing regions. Note the absence of filling of the subcapsular sinuses.

B. Localized involvement of left para-aortic nodes with multiple filling defects is apparent. The size of individual nodes is within normal limits. This appearance is not uncommon in Hodgkin's disease.

Figure 8 Giant follicular lymphoma. Extensive enlargement and a reticular appearance of the external iliac nodes and femoral nodes are noted. There was no involvement of para-aortic nodes.

Measurements

The position of the retroperitoneal lymph nodes is closely related to the course and position of the abdominal aorta and inferior vena cava. Slight displacement of these anatomic structures is directly reflected in the position of the nodes. Enlargement of the lymph nodes and lymphomatous involvement of the perilymphatic soft tissue produce abnormal relationship of the lymph nodes to the adjacent structures, thus producing abnormal position of the nodes in relationship to the major vessels and spine. Three measurements were obtained from 24-hour anteroposterior and lateral lymphographic films and correlated with lymphographic diagnoses (Table V). A 36 inch target-film distance was used and no correction was made for magnification.

Table V. Size and Position of Nodes in Lymphoma

	Number of Cases	Mean (cm.)	SD
Size of Nodes			
Normal	60	1.9	0.42
Abnormal	60	3.1	0.96
Proposed Normal Range: 2.5 cm. or less			
Measurement A			
Normal	60	2.0	0.61
Abnormal	60	3.3	1.31
Proposed Normal Range: 3.0 cm. or less			
Measurement B			
Normal	60	0.9	0.47
Abnormal	60	1.8	1.24
Proposed Normal Range: 2.0 cm. or less			
Measurement C			
Normal	60	1.0	0.52
Abnormal	60	2.2	1.17
Proposed Normal Range: 2.0 cm. or less			

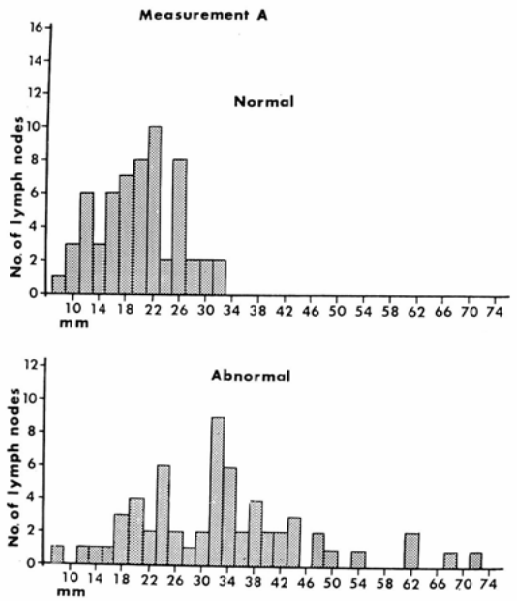
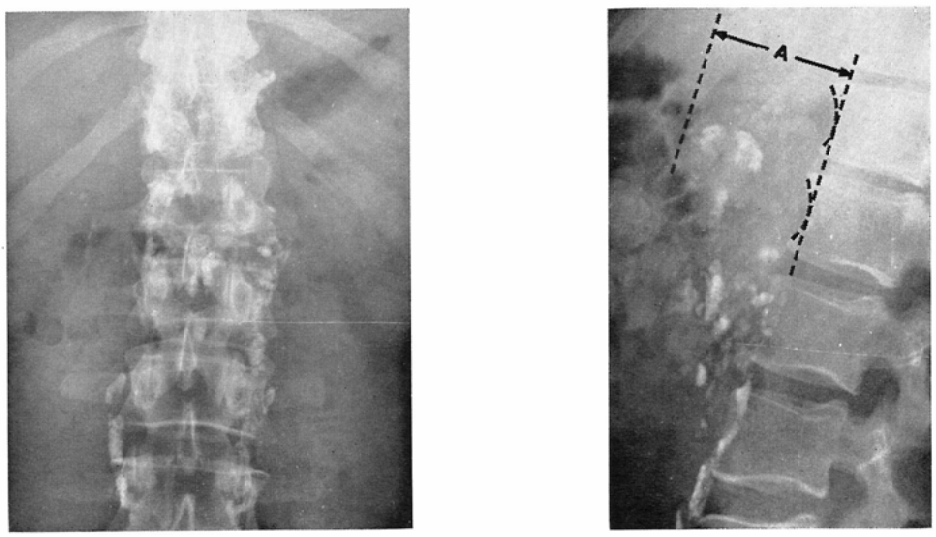


Fig. 9. The anterior spine to node distance(Measurement A). This distance is the measurement on the crosstable lateral film from the anterior surface of the lumbar vertebral body at its midpoint to the anterior surface of the adjacent node group. The mean values in 60 normal and 60 abnormal studies were 2.0 cm. and 3.3 cm. with standard deviations of 0.61 and 1.31, respectively. When 3.0 cm. was considered as the upper limits of normal, there were only two normal cases with a large measurement.

1. *Measurement A (Anterior Spine to Node Distance):* Measurement A is defined as the distance from the anterior surface of a lumbar vertebral body at its middle point to the anterior surface of the node group on a cross table left lateral lymphographic film. The most anteriorly located nodes were taken for measurements. These nodes were usually closely related to the inferior vena cava, representing pre-caval or juxtacaval nodes. The anterior para-aortic nodes were usually projected slightly posterior to these node groups in the true lateral projection.

The mean values of Measurement A for 60 normal lymphograms and 60 abnormal studies were 2.0 cm. and 3.3 cm. with standard deviations of 0.61 and 1.31, respectively (Table V). In Figure 9, both groups were plotted on a distribution curve. There was a wide range distribution in the abnormal group, while all cases of the normal group fell below the range of 3.2 cm. When 3.0 cm. was considered as the upper limits of normal, there were only two false positives in this group of 60 cases and 36 cases in the abnormal group were beyond this range (Figs. 10A & B, 11A & B).

2. *Measurement B (Right Lateral Spine to Node Distance):* Measurement B is the distance from the right lateral border of a lumbar vertebral body at its middle point to the most lateral border of the right juxtacaval node group (Fig. 12). The greatest distance was chosen from measurements at several lumbar vertebral levels. The mean values were 0.9 (SD 0.42) and 1.8 (SD 1.24) for nomal and abnormal groups (Table V). Distribution curves are shown in Figure 13. From this figure 2.0 cm. would be considered as the upper limits of normal for Measurement B.



(A) (B)

Fig. 10. Hodgkin's disease.

A. Anteroposterior view shows a normal appearance, size, and position of the para-aortic nodes.

B. Lateral film demonstrates multiple lymph nodes extending far anteriorly to D12-L2. Measurement A is 5.5 cm. The inferior vena cavogram was normal. If the lateral film had been omitted, correct evaluation of this proved positive case would have been difficult.

(A) (B)

Fig. 11. Lymphosarcoma in a 15-year-old boy.

A. Lateral view of initial lymphogram (1-11-62) shows no significant abnormality in the individual nodes. Measurement A is 2.3 cm., but lymph nodes at D12-L1 are located somewhat anteriorly compared with nodes at lower levels. Study was interpreted as negative.

B. Follow-up film (5-10-62) reveals definitely abnormal distance (3.4 cm.). Individual nodes remain normal in appearance.

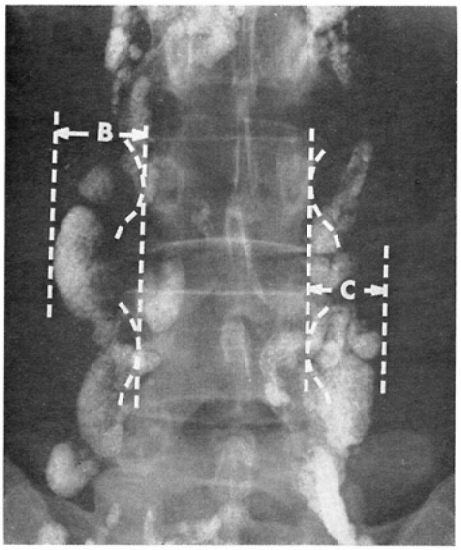


Fig. 12. Spine to node distances. The right lateral spine to node distance (Measurement B) is the measurement from the right lateral border of a lumbar vertebral body at its midpoint to the most lateral border of the right juxtacaval node group. In this case it is 2.5 cm., beyond the normal limit. The left lateral spine to node distance (Measurement C) is the same measurement on the left side and is within the normal range, 1.8 cm.

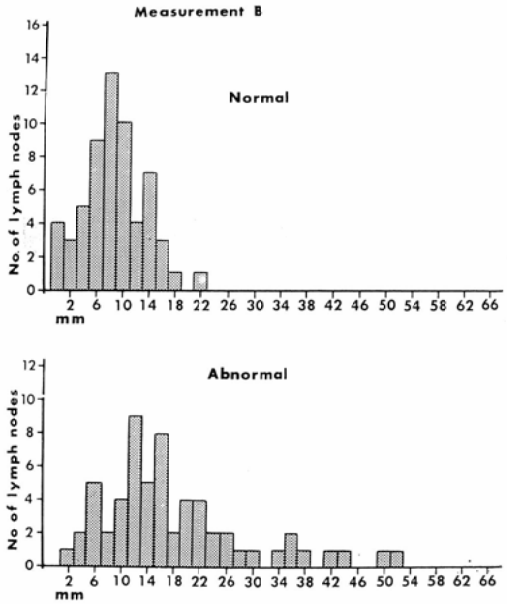


Fig. 13. Right lateral spine to node distance (Measurement B). Distribution curves on 60 normal and 60 abnormal cases. This is the measurement from the right lateral border of a lumbar vertebral body at its midpoint to the most lateral border of the right juxtacaval node group. The proposed upper limit of normal is 2.0 cm.

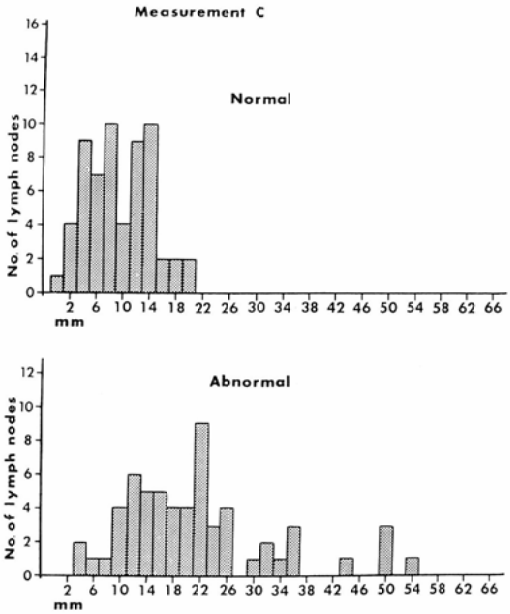


Fig. 14. Left lateral spine to node distance (Measurement C). Distribution curves on 60 normal and 60 abnormal lymphograms. This is the measurement from the left lateral surface of the mid point of the vertebral body to the most lateral border of the left para-aortic node groups. The upper normal limit is 2.0cm.

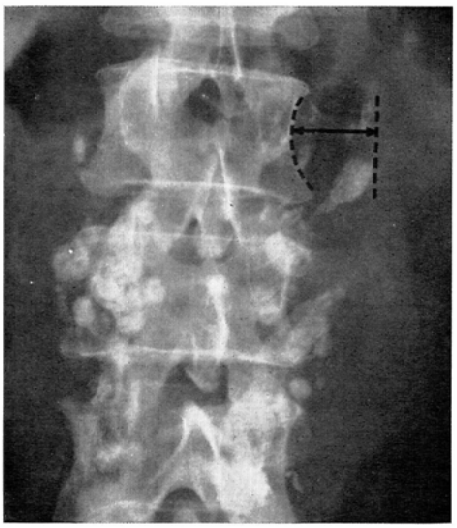


Fig. 15. Giant follicular lymphoma. The common iliac and para-aortic nodes were normal, but the left lateral spine to node measurement was 2.4 cm. at the level of L2. The lymphogram was initially interpreted as negative, but exploratory laparotomy revealed positive nodes at the same region.

3. *Measurement C (Left Lateral Spine to Node Distance):* This measurement is similarly defined as the distance from the left middle lateral border of a lumbar vertebral body to the lateral surface of the left lateral para-aortic node group (Fig. 12). The measurements are plotted on distribution curves for normal and abnormal groups (Fig. 14). Mean values were 1.0 cm. (SD 0.25) and 2.2 cm. (SD 1.17) for normal and abnormals. (Table V). The proposed normal range for Measurement C is 2.0 cm. All the normal nodes fell within this range and 28 of 60 abnormal nodes were localized outside this value (Fig. 15). Occasionally a tortuous aorta produced slightly lateral position of the nodes.

4. *Size of the Lymph Nodes:* Measurement of the greatest diameter of a lymph node was made on the largest node in the para-aortic and internal and common iliac node groups on anteroposterior films. The inguinal and external iliac nodes were excluded from the selection since these nodes are frequently involved by inflammatory processes. Distribution curves are shown in Figure 16. There was considerable variation in size in the abnormal group, but 58 of 60 normal nodes were below 2.5 cm. in diameter which is the proposed normal range for the size of the lymph nodes. Mean values were 1.9 cm. and 3.1 cm. for normal and abnormal group, the standard deviation being 0.42 and 0.96, respectively (Table V).

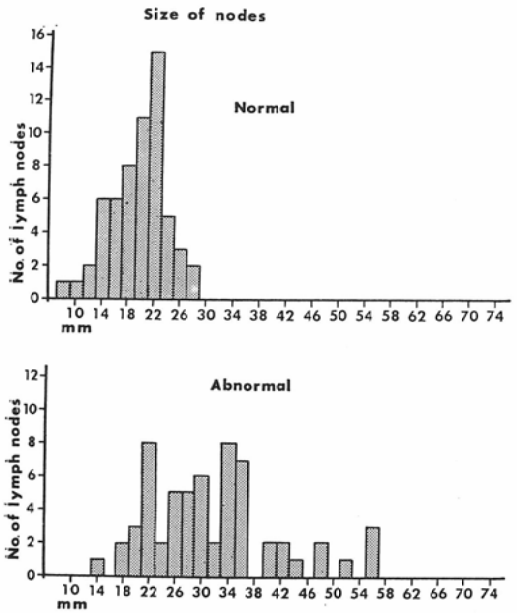


Fig. 16. Size of the lymph nodes in 60 normal and 60 abnormal lymphograms. Mean values were 1.9 cm. and 3.1 cm. for the normal and abnormal group, with a standard deviation of 0.42 and 0.96, respectively. Fifty-eight of 60 nodes were 2.5 cm. or below in diameter. This is the proposed normal range for node size.

Diagnostic Accuracy

The overall diagnostic accuracy of lymphography in malignant lymphoma was 80.6% (Table II). Lymphosarcoma and reticulum cell sarcoma presented slighly less difficulty in interpretation (87.1% and 82.1%, respectively) as compared with Hodgkin's disease (78.8%) and giant follicular lymphoma (75.0%). There was a statistically significant difference between the accuracy in lymphosarcoma and in the other histologic types.

In order to demonstrate difference of the interpreters' opinion and to confirm the statistical observation that lymphosarcoma and reticulum sarcoma presented less difficulty than in other histologic types,

Table VI. Retrospective Analysis of Lymphoma

A. Individual Interpretation

	Radiologist	Negative	Indeterminate	Positive
Group I				
(30 positives)	A	2	1	27
	B	1	1	28
	C	0	2	28
	D	0	2	28
	E	0	2	28
Group II				
(30 negatives)	A	23	4	3
	B	21	2	7
	C	20	7	3
	D	20	9	1
	E	24	6	0
Group IV				
(30 false negatives)	A	12	9	9
	B	9	7	14
	C	8	12	10
	D	9	15	6
	E	6	10	14

B. Group Interpretation

	Total	Negative	Indeterminate	Positive
Group I (positives)	30	0	1	29
Group II (negatives)	30	24	6	0
Group IV (false negatives)	30	9	10	11

5 radiologists reviewed 90 lymphograms which consisted of 30 arbitrarily selected cases from Group I (Positive), Group II (Negative), and Group IV (False negative). They recorded their diagnoses as negative, indeterminate, and positive. There was a wide variation in the interpretation of Group II and IV, but the diagnoses in Group I by each radiologist coincided very well (Table VIA), indicating that positive lymphograms were diagnosed with considerable ease. When the difference in interpretation among five radiologists was reconciled by a conference, there was significant improvement in the diagnostic accuracy, eliminating all the misinterpretations in Group I and II and some in Group IV (Table VIB).

Diagnostic accuracy in each histologic type made at the conference of the five radiologists is shown in Table VII. There was some difficulty in the diagnosis of Hodgkin's disease, while lymphosarcoma and reticulum cell sarcoma were diagnosed with relative ease.

Comparison of Inferior Vena Cavography and Lymphography

Retrospective analysis of inferior vena cavography was performed without information of lymphograms, since the initial interpretations of inferior vena cavograms had been frequently influenced by the results of lymphography.

Table VII. Retrospective Analysis of Lymphoma by Histologic Type

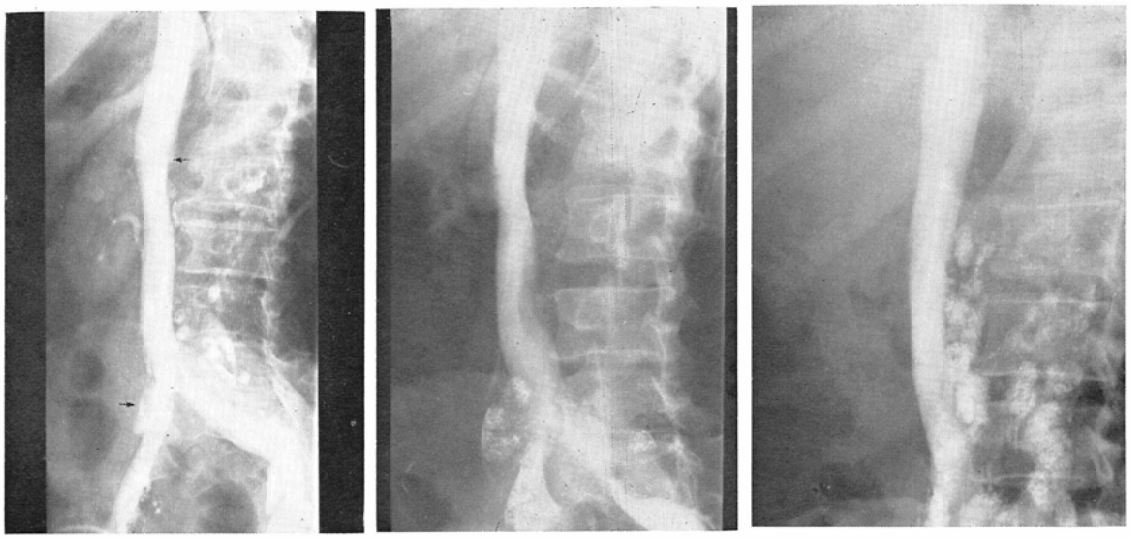
Type	Group	Total	Negative	Indeterminate	Positive
Hodgkin's Disease (total 49)	Group I (positive)	12	0	1	11
	Group II (negative)	18	15	3	0
	Group IV (false negative)	19	7	7	5
Reticulum Cell Sarcoma (total 20)	Group I (positive)	8	0	0	8
	Group II (negative)	6	6	0	0
	Group IV (false negative)	6	1	2	3
Lymphosarcoma (total 16)	Group I (positive)	8	0	0	8
	Group II (negative)	5	3	2	0
	Group IV (false negative)	3	1	0	2
Giant Follicular Lymphoma (total 5)	Group I (positive)	2	0	0	2
	Group II (negative)	1	0	1	0
	Group IV (false negative)	2	0	1	1

Table VIII. Results of Inferior Vena Cavography in Comparison with Lymphography

	Lymphography	Total	Inferior Vena Cavography Positive	Negative
Group I	Positive	71	55	16
Group II	Negative	77	3	74
Group III	False Positive	10	0	10
Group IV	False Negative	27	4	23
	Total	185	62	123

In 185 out of the present series of 206 patients, inferior vena cavography was performed as a part of the preliminary work-up of malignant lymphoma (Table VIII). There were 62 positive studies and 123 were interpreted as negative (Fig. 17A, B & C).

Significant contribution of inferior vena cavography was seen in 7 cases which revealed positive inferior vena cavograms in the presence of negative or false negatire lymphogvams. They were 6 Hodgkin's diseases and 1 reticulum cell sarcoma. Five of these revealed displacement or concave impression of the inferior vena cava above the cisterna chyli, while there was impression of the inferior vena cava at the confluence of the left renal vein in 2 cases. Inferior vena cavograms were negative in 16 of 71 positive lymphograms. Although inferior vena cavography was frequently supplementary to or confirmatory of information obtained from lymphography, this procedure alone did not give sufficient information for management of malignant lymphoma.



(A) (B) (C)

Fig. 17. Negative and positive inferior vena cavograms in the right posterior oblique projection.

A. Negative inferior vena cavogram in a false positive lymphogram (See Fig. 1). A slightly enlarged node with a filling defect (arrow) proved to be a post-inflammarory node. Note a washout defect from the left renal vein (arrow head).

B. Lymphosarcoma showing multiple concave impressions on the inferior vena cava and common iliac veins.

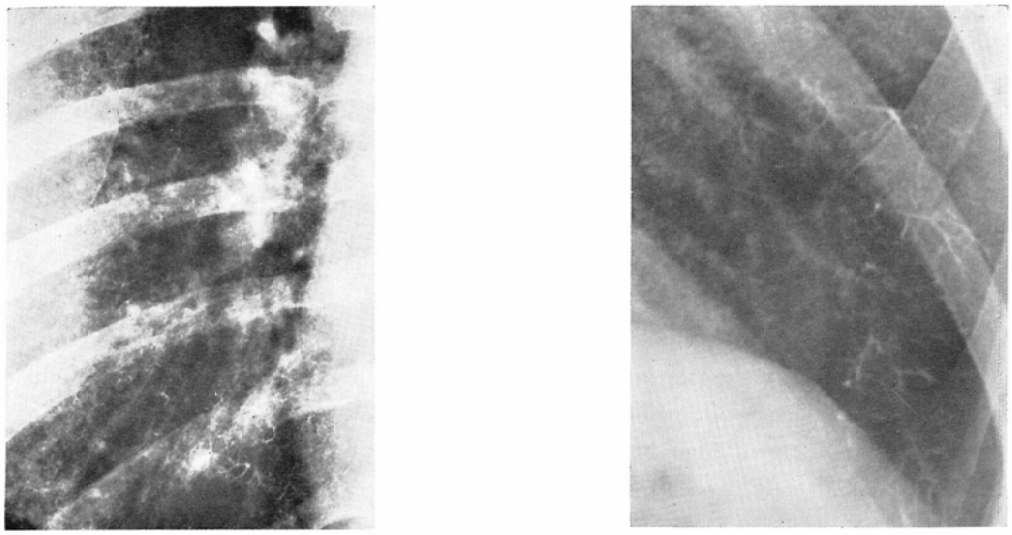
C. Hodgkin's disease with smooth lateral displacement of the inferior vena cava.

Complications

Most frequent complications of lymphography were fine pulmonary stippling observed on 24 or 48 hour chest roentgenograms. This complication was demonstrated in more than 50% of 206 patients. Pulmonary stippling was frequently followed by patchy peribronchial infiltrates, especially in the lower lung fields on overpenetrated chest films. These infiltrates usually cleared over a 2 to 3 day period without residual fibrosis. Pulmonary stippling was sometimes associated with pyrexia, cough, dyspnea, chest pain or palpitation of a minor degree. In 3 patients of this series, there was arborizing pulmonary embolization which probably represented extreme degree of pulmonary stippling. Two representative cases were shown (Fig. 18A & B). One of these 3 patients developed pulmonary infarct in the left lower lung associated with severe chest pain. Pulmonary infarct in this patient cleared over one month with minimal residual parenchymal scarring.

In regard to severe pulmonary complications, 2 patients developed immediate hypotension, cyanosis, chest pain, and dyspnea which required prolonged intensive care. Both patients survived. There were associated pulmonary diseases in both patients: atelectasis of the right lung in one and marked emphysema in the other.

Local complications such as wound infections, lymphangitis and edema of the lower extremities were observed in a small number of patients. All of them were controlled by symptomatic treatments. Der-



(A) (B)

Fig. 18. A & B. Extensive arborizing pulmonary embolization in 2 patients. Chest films were exposed immediately after completion of injecting 10 cc. of Ethiodol in each leg.

matitis was seen in 2 patients approximately 10 days after lymphography. Both patients responded to symptomatic therapy.

Discussion

In spite of the favorable acceptance of lymphography for diagnosis and management of malignant lymphoma, diagnostic accuracy has not been evaluated in a large material partly due to the difficulty of verifying the diagnosis either by surgery or follow-up. According to a survey carried out by Koehler et al. (26), in which 22 of 29 investigators replied the diagnostic accuracy for malignant lymphomas was more than 80%. In preliminary results with a small number of cases, several investigators (12, 24, 35, 38, 44) reported a high accuracy of this method in the diagnosis of lymphoma. The author's results of 80.6% in 206 pathologically and clinically verified cases are consistent with the above reports. In the author's experience positive lymphograms almost always indicated that the visualized lymph nodes are involvedby lymphomatous diseases with the exception of a few cases with post-inflammatory changes. Negative lymphograms, however, occasionally proved to be positive on follow-up studies or by biopsy as has been shown in 30 false nagative cases. In the analysis of these false negatives, 11 cases viewed retrospectively represented probably misinterpretations which were mostly encountered in the earlier lymphograms, thus suggesting even lower incidence of "true" false negatives. Nevertheless, our interpretation of normal lymphograms was not as accurate as in positive studies. In order to accommodate such cases, a category of "equivocal" is now used in addition to "positive" and "negative". Patients in this category should have exploration of the retroperitoneal space with histologic verification of the presence or absence of disease. In this way, precise staging may be accomplished.

Rapid development of abnormal nodes on follow-up studies as observed in reticulum cell sarcoma and lymphosarcoma are probably explained by the natural course of the disease. Average life of the

patients with these two histologic types is usually less than one year from the initial diagnosis, whereas average life in Hodgkin's disease and giant follicular lymphoma are more than three years (32). The natural course of disease is also reflected in lymphographic patterns of each histologic type, in that Hodgkin's disease sometimes shows localized involvement of the para-aortic nodes, while reticulum cell sarcoma and lymphosarcoma usually reveal extensive involvement of retroperitoneal and iliac nodes. Extensive enlargement of the lymph nodes are more frequently seen in the latter two conditions.

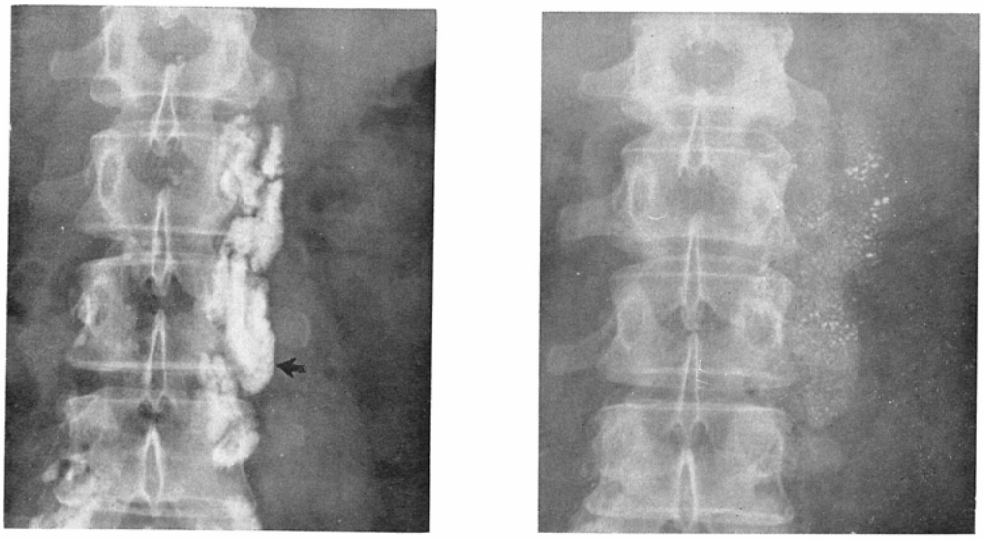
One of the difficulties in interpretation of lymphograms is the fact that there is no clear-cut borderline between abnormal and normal lymph nodes. Normal lymph nodes in the para-aortic and common iliac regions frequently contain very small filling defects and slight marginal irregularity on close inspection (6, 43). The normal nodes may appear slightly foamy frequently due to a previous inflammatory disease. Standard roentgenograms as presented in this report were of considerable help in evaluation of borderline cases. Apparent filling defects which are produced by superimposition of separate small lymph nodes were frequently assessed by laminograms and various projections (1, 5, 6). Evaluation of the size of a lymph node may also be difficult. Normal nodes in para-aortic or common iliac regions may measure nearly 2.5 cm. in the greatest diameter; nodes above this measurement should be considered abnormal or suspicious in these areas. A previous report (8) suggests that normal nodes fall within the range of 2.0 cm. in the greatest diameter.

In an ingenious approach to neoplastic involvement of lymph nodes, Wiljasalo (47) determined a "projection difference index" which indicated whether nodes were flat, cylindrical, or globular. He assumed that nomal nodes were flat. Using films in the anteroposterior and both oblique projections, he measured the width of the nodes. The index was based on a formula in which the difference between the maximum and the minimum width was divided by the minimum width. If the difference was small, it generally meant that the node was globular or cylindrical, while if the width was large, it implied a flat node. He found a high correlation between carcinomatous metastases and a low projection difference index (below 20%), supporting the presence of round or globular nodes when tumor was present. Unfortunately, the projection difference index was by no means as useful in lymphoma. More lymphomatous nodes had an index above 20% than below, although there was a significant group with an abnormal projection difference index as well.

As reported by others (6), evaluation of external iliac and femoral nodes was extremely difficult because of the postinflammatory change. Filling defects per se in these areas are not positive signs unless they are accompanied by markedly enlarged or foamy lymph nodes.

A good correlation of histologic and radiographic diagnosis has been reported (42, 45). Although there are certain characteristic patterns of Ethiodol deposition in the nodes of malignant lymphoma, there were some cases in which lymphographic patterns were not characteristic of any histologic type and other cases in which the appearance simulated different histologic types. Histologic differentiation by lymphography is usually of academic interest and has not been helpful in the management of patients in our experience. We have not been able to duplicate the high correlation between lymphographic and microscopic diagnosis reported by Wiljasalo (47). It is not entirely clear that the 40 positive cases which he analyzed were treated as total unknowns, without prior cognizance of the histologic diagnosis.

Among the spine to node measurements described in this report, the anterior distance (Measurement A) was the most useful on the initial interpretation. Five of 30 false negative cases showed a value of



(A) (B)

Fig. 19. Hodgkin's disase.

A. Initial lymphogram (2-2-65) was considered negative, but in retrospect there are several large nodes in the left para-aortic region at L3-4, the largest node measuring 3.0 cm. in the greatest diameter (arrow).

B. Eight months later (10-4-65) there were markedly enlarged nodes with grossly abnormal lateral spine to node distance.

more than 3.0 cm. for Measurement A, whereas 2 cases in this group revealed an abnormal lateral distance (Measurement B and C). On follow-up studies, Measurement B and C were of particular value (Fig. 19A & B). Since Ethiodol remains in the lymph nodes for sustained periods (9), comparative data are frequently available. Slight changes in size and position of nodes are of considerable importance since the gradual loss of Ethiodol renders the interpretation of internal architectural change more difficult. As might be expected, these values are not always diagnostic, and should be considered as useful adjuncts in diagnosis. The measurements lose their reliability in patients with severe scoliosis or a tortuous aorta. In addition, true lateral and anteroposterior films are essential for the measurements.

It is of interest that a group of five radiologists have done much better in interpretation of lymphograms than any individual radiologist. This is probably because lymphographic interpretation is frequently subjective. It is our routine practice that two or more radiologists review the study independently and the difference in interpretation among the radiologists are reconciled in conference. Since this approach was initiated, we have been able to improve our diagnostic accuracy of lymphography to some extent.

Most important contribution of inferior vena cavography is in patients with localized involvement of right paravertebral nodes above the cisterna chyli where the lymph nodes are not visualized routinely by lymphography (37). There were five such cases in this report and they were all proven to be localized involvement by Hodgkin's disease. When perilymphatic infiltration is present in the right paravertebral area without involvement of adjacent nodes, inferior vena cavography was an important supplementary diagnostic method as was seen in two patients in this report. Except for these seven cases, there were

always abnormal lymphograms in the presence of positive inferior vena cavograms. However, information obtained from the inferior vena cavograms frequently helped to determine the field size to which radiotherapy is given (21, 27, 28). Negative inferior vena cavography frequently obviated necessity of an exploratory laparotomy when there were equivocal nodes in the right paravertebral areas, since this type of combination pointed toward uninvolved lymph nodes (37). The inferior vena cava was not affected by a left paravertebral mass even when considerably large. Nevertheless confirmatory value of the inferior vena cavograms was considerable in this study (28).

Ethiodol pulmonary embolization or miliary stippling in the lungs have provoked many basic research (2, 3, 10, 13, 16, 17, 25, 40). In animal experiments performed at our laboratory and detailed elsewhere (40), it was found that intravenous injection of Ethiodol in a dose of 0.05 cc/kg, and intralymphatic injection of 0.2 cc/kg did not produce any evidence of Ethiodol pulmonary embolization on chest films. If the dogs were sacrificed and an x-ray of the lung specimen obtained, there was marked pulmonary embolization on the films of the specimen. It can be assumed that there is extensive pulmonary artery or capillary embolization in man even in the absence of miliary pattern on chest x-rays. With larger volumes, stippling or arborizing pattern of pulmonary embolization was observed. In some dogs this

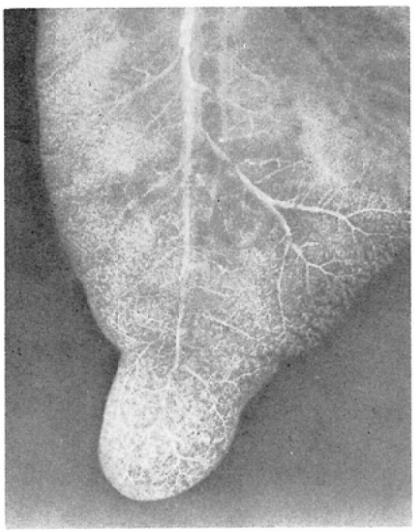


Fig. 20. Extensive arborizing pulmonary emboli on a roentgenogram of lung specimen of a dog 72 hours after rapid intravenous injection of 21.8 cc. (1.0 cc/kg body weight) of Ethiodol. The chest x-ray was normal shortly before the sacrifice of the dog.

disappeared in 5 minutes to 2 hours, while in others it persisted beyond that length of time. If a dosage was greater than 0.25 cc/kg for intravenous injection and 0.7 cc/kg for intralymphatic injection, arborizing pulmonary embolization was almost invariably observed. This was usually followed in 2 to 4 hours by patchy, confluent parenchymal infiltrates superimposed on the arborizing pattern throughout the lungs, most of which gradually cleared over 24 to 72 hours. But a roentgenogram of the lung specimen showed extensive arborizing pulmonary embolization (Fig. 20). The patchy pulmonary infiltrates in dogs are probably chemical pneumonitis which corresponds to the clinically observed patchy peribronchial infiltrates in the lower lung fields on 24 hour chest films. These infiltrates in patients usually clear over a 2 to 3 day period without any residual fibrosis.

Severe complications of lymphography in 2 patients reported in this communication are probably

due to marked pulmonary embolization in association with the pre-existing pulmonary abnormality. The clinical course was that of cardiopulmonary collapse. Twenty cc. of Ethiodol were injected in each case. Severe complications described in the literature are similar to these two patients and usually associated with injection of a large amount of contrast agent or had pre-existing pulmonary conditions (11, 15, 19, 30). Fuchs (11) reported two similar cases with cardiopulmonary collapse in which more than 20 cc. of oily media was injected, but no pre-existing pulmonary condition was present. Koehler et al. (12) described two patients who developed severe pulmonary edema after lymphography. Their two patients had received irradiation to both lungs amounting to a dose of 1,700 rads. One of their two patients expired. They did not state the exact amount of contrast media used. Desprez-Curley et al. (15) reported a death in a child weighing 30 kg. in whom 25 cc. of Ultra-Fluid Lipiodol had been injected. There is also a report on a fatal complication due to cerebral Ethiodol embolization following lymphography (30). Twenty cc. of Ethiodol were used in each leg and collateral vessels were demonstrated on the initial abdominal films.

All the severe complications in the literature are related to severe pre-existing pulmonary diseases or excessive amount of contrast media utilized (15, 19). It is also our experience that pulmonary embolization is more frequent and severe when the lymphatic collateral vessels are demonstrated on the initial pelvic and abdominal films (2). In order to minimize the severe complications, it is of utmost importance to reduce the amount of Ethiodol as much as possible. Fluoroscopic and radiographic monitoring should be an essential part of lymphography, so that injection can be terminated as soon as the cisterna chyli is visualized or abnormal lymphaticovenous communication is demonstrated. In some adults with small lymphatic capacity, 5 cc. of Ethiodol injected to each leg have produced good diagnostic roentgenograms. Prelymphogram chest films should be always obtained.

Summary and Conclusions

Two hundred and six lymphograms on malignant lymphoma with at least one year follow-up were reviewed and the following observations were made:

1. Diagnostic accuracy of malignant lymphoma was 80.6%. Lymphosarcoma and reticulum cell sarcoma gave less difficulty in interpretation than Hodgkin's disease and giant follicular lymphoma.

2. Among the 30 "false negative" cases, most Hodgkin's disease developed abnormal retroperitoneal nodes between 6 and 12 months, whereas all reticulum cell sarcoma and lymphosarcoma revealed positive nodes within 6 months.

3. Considering the number of the general group, more cases with Hodgkin's disease and giant follicular lymphoma were noted in "false negative" group than the cases with reticulum cell sarcoma and lymphosarcoma.

4. Evaluation of degree of foamy appearance and filling defects frequently helps to establish a definite diagnosis.

5. Persistent visualization of the lymphatics on the 24-hour films occasionally suggests an abnormal lymphogram in the absence of other findings.

6. It was possible to make specific differentiation of types of lymphoma in 41 of 85 positive studies with incorrect diagnoses in 15 cases and indeterminate pattern in 29. Common lymphographic patterns in each histologic types are:

A. Reticulum cell sarcoma and lymphosarcoma—a reticular and granular background pattern in markedly enlarged nodes with or without subcapsular filling.

B. Hodgkin's disease and giant follicular lymphomas—

1. There may be slightly foamy appearance in minimally enlarged nodes. All the retroperitoneal nodes tend to be involved.
2. There may be numerous filling defects in normal or slightly enlarged nodes. Involvement of all the retroperitoneal nodes is to be expected.
3. There is occasionally localized involvement in retroperitoneal nodes.

7. Certain measurements were helpful in the diagnosis of equivocal cases. The proposed normal limits are:

Measurement A:	3.0 cm. or less
Measurement B:	2.0 cm. or less
Measurement C:	2.0 cm. or less
Size of Nodes:	2.5 cm. or less

8. Inferior vena cavography had supplementary value in the interpretation of lymphograms. There were 7 positive inferior vena cavograms in the presence of negative lymphograms.

9. Severe complications are related to pre-existing pulmonary conditions or use of an excessive amount of contrast media.

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