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## Summary

1. Radiographic morphology and morphometry of retroperitoneal lymph nodes has been described in patients with each of the common presenting histological subtypes of Hodgkin's Disease.

2. In addition to well known lymphographic features of Hodgkin's Disease many less florid changes have been described in the radio-opaque images of pelvic and retroperitoneal lymph glands. Such non-specific findings have been seen in the absence of histological evidence of Hodgkin's Disease in the same nodes, and may be related to abnormal lymphoreticular function preceding or concurrent with early neoplastic changes (19). Their significance with respect to immune mechanisms is not yet known.

3. Because of current ignorance of the basic pathogenesis of Hodgkin's Disease, in vivo lymphographic study of contrast containing intranodal sinusoids of many glands, and in vitro histological study of individual lymph node samples obtained at biopsy or laparotomy evaluate different parameters of abnormality, and are at present complementary.

4. In this series lymph node architecture and the topography of adenopathy suggest two distinct patterns of involvement in Hodgkin's Disease.

5. A practical method of dividing the majority of new patients with Hodgkin's Disease into two groups for further study is described.

## Introduction

Despite some inherent limitations (7, 12, 16), lymphography, by display of many groups of lymph glands not readily accessible to clinical examination, has proven a useful adjunct to accurate premanagement assessment of patients with malignant lymphoma (5, 21). In Hodgkin's Disease, increasing use of laparotomy for diagnostic purposes indicates that histology is more accurate than radiology when equivocal changes are present in aortic nodes (16). However in general, the accuracy of interpretation of lymphograms in identification of diseased lymph nodes has been confirmed (14). Some difficulty in obtaining accurate comparison of histological and radiological findings has been encountered, and sampling at diagnostic laparotomy may not always provide definitive information about the majority of aortic glands. In a rather neglected paper, *Slaughter* et al. (29) recorded that from the same region normal, "paragranulomatous", "granulomatous", and eosinophilic infiltrated lymph nodes were removed at surgery (20). For these reasons, at the present time, lymphography by displaying many adjacent groups of lymph glands, remains a valuable guide to optimal sites of biopsy and provides assessment of many nodes less accessible to the surgeons (14).

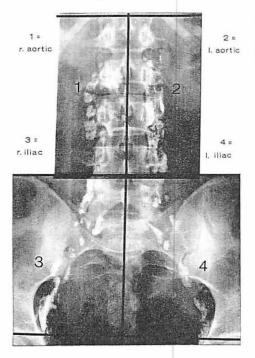
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The radiographic appearances, and case reports illustrating lymphographic findings in Hodgkin's Disease have frequently been reported (2, 12, 33, 35, 36), but there have been few detailed accounts of the radiographic features of lymph nodes. This study analyses the findings on lymphograms, chest radiographs, and clinical examination of the superficial lymph node sites, in 104 patients with the common presenting histological subtypes of Hodgkin's Disease (22, 23, 24). Although only 39 of the 104 patients to be described had acceptable radiological criteria for the diagnosis of lymphomatous infiltration with subsequent alteration in staging, many other morphological features of the radio-opaque images of retroperitoneal lymph nodes were found. With the present lack of knowledge both of lymph node appearances during immune reactions, and of the significance of immunological stimulation, depression and auto immunity in the basic pathogenesis of malignant lymphoma (19), it is possible that the radiological features to be described are crude macroscopic evidence preceding or accompanying the diagnosis of malignancy by present histological criteria.

## Material and Methods

Clinical records and radiographs of 104 patients were reviewed. All had been diagnosed by biopsy as suffering from Hodgkin's Disease. Lymphocyte predominance (L. P.), nodular sclerosis (N. S.), or mixed cellularity (M. C.) were diagnosed following review of the histological sections. All patients had standard P. A. and lateral chest radiographs, A. P. linear tomography of the mediastinum, and bilateral lower extremity lymphography performed by the usual technique (17, 34). A total dose of approximately 12 mls. Ultra Fluid Lipiodol was injected at a rate of 1 ml per 8 minutes with monitoring of flow by fluoroscopy and radiography to obtain optimal demonstration of pelvic and aortic lymph nodes. No patient had prior radiation to the pelvis or



abdomen, or recent treatment with steroids or drugs known to influence lymphoreticular tissues. No child under age of 12 was included because of possible differences in the natural history of Hodgkin's Disease in children (11, 13). 104 consecutive patients fulfilling these criteria who had successful bilateral lymphographic studies and available case records form the material for this analysis.

Fig. 1 Female (23 yrs) with Hodgkin's Disease (N. S. type). Composite radiograph from individual films of pelvic and aortic lymph nodes shows the lines of division into four regions.

The presence of palpable enlarged lymph nodes in the superficial groups was recorded from the case sheets in four anatomical regions (supraclavicular, upper cervical, axillary, inguinal). From chest radiographs, the presence or absence of abnormality of the mediastinum was assessed. A. P. linear tomographs of the mediastinum were available to confirm the plain film findings and all equivocal appearances were regarded as normal. The location in the mediastinum of soft tissue masses was assessed, and the presence or absence of hilar abnormality recorded.

Separate A.P. radiographs of the abdomen and pelvis following lymphography were divided into regions as in Fig. 1. In each region morphological features and measurement of opacified nodes were recorded in the following terms:

1. The contours of the margin of the majority of Tymph nodes were assessed as regular, or irregular with a 1 and 2 + grading (Fig. 2a).







Fig. 2a Contour

regular

irregular +

irregular ++

2. The presence or absence of filling defects within the opacified lymph node parenchyma was noted; round or oval discrete defects were recorded by size as greater or less than 2 mm. in long diameter, or both (Fig. 2b).













discrete <2mm discrete >2mm

discrete both 〈 〉and 2 mm confluent + c

confluent++

- Fig. 2b Filling defects
- 3. Irregular areas of non-opacification, (excluding the hila) were termed confluent filling defects, and the size and number recorded on a 1 + to 3 + scale (Fig. 2b).
- 4. The number of lymph nodes present was assessed as increased, normal, or decreased, with due consideration for variation known to exist within the range of normal (Fig. 2c).

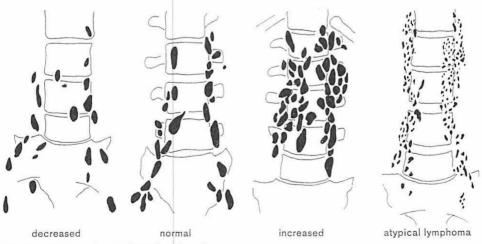


Fig. 2c Node number and atypical lymphoma pattern

- 5. Atypical lymphoma patterns (18) defined for this study as an absence of formed lymph nodes throughout the region were noted (Fig. 2c).
- 6. The surface area of lymph nodes was measured using a planimeter\*, from paper tracings of the opacified glands.

## Results

# Clinical Examination, Chest Radiographs, and Biopsy Sites

The sites at which enlarged lymph nodes were detected by palpation and the presence of mediastinal abnormality on chest radiographs are illustrated for each of the three subtypes in Fig. 3. Biopsy sites are documented in Table 1.

		vical Upper	Axilla	Groin	Abdomen	Mediastinum	Total
L. P.	10	8	6	6	1		31
N. S.	29	1	1		1	2	34
М. С.	26	3	6	3		1	39

Table 1 Distribution of sites of diagnostic biopsy in 104 patients.

In 31 patients with L.P., involvement of cervical, axillary, and groin nodes was relatively common, and biopsies were taken from these superficial lymph node groups in 20 of the 31 patients. Mediastinal involvement was uncommon in L.P., being detected in only two patients. By contrast, a relatively larger number of those with N.S. had palpable supraclavicular nodes, and biopsy from this site was performed in 29 of 34 patients. Mediastinal involvement was detected in the majority of these patients (29 out of 34). It is of interest that in two patients with N.S., no palpable superficial lymph nodes were found, and constitutional upset was the indication for chest x-ray. Diagnosis in both of these patients was made following biopsy direct from the soft tissue masses demonstrated in the mediastinum on chest radiographs. Axillary lymph node enlargement was common in both L.P. and N.S. Enlarged inguinal lymph nodes were present in six of those with L.P., and in none of those with N.S. Thus in L.P., the majority of patients presented with enlarged superficial lymph nodes and mediastinal abnormality was uncommon, while in N.S., the majority presented with enlarged supraclavicular lymph nodes and abnormality of the mediastinum occurred frequently.

In the 39 patients with M.C., involvement of both the superficial lymph node sites and the mediastinum was often found. Biopsy was most frequently from supraclavicular lymph nodes, although in twelve patients other superficial groups were the sites of biopsy. In one patient the diagnosis was made direct from the mediastinum. Thus in many cases of M.C., the findings resemble those occurring in L.P., while in others, the topography was similar to that found in N.S.

## Lymph Node Morphology

Architectural changes in the patterns of contrast medium within the parenchyma of the lymph nodes were assessed in each region. The findings for the left aortic nodes

<sup>\*</sup> Ott-planimeter 4262 Keuffel Esser Company.

(which for anatomical reasons are better defined and show fewer normal irregularities than pelvic nodes [9]), are presented in Table 2.

		Contour			Filling Defects					Node Number		
		Regula	r +	Irregular ++		Discrete >2 mm	≷2 mm	Conf +	luent ++	_	N	+
L. P.	31	26	5	0	4	0	0	1	2	0	25	6
N. S.	34	11	20	3	24	0	1	6	5	4	25	5
M. C.	39	21	16	2	15	4	1	3	6	0	31	8

Table 2 Radiographic features of left aortic lymph nodes.

L.P. - Eight of the 31 lymphograms were considered abnormal by commonly accepted criteria (1, 8, 36), namely regional enlargement of lymph nodes and coarse granular pattern of the parenchyma. Three of these showed confluent filling defects in the storage patterns. The vast majority of lymph glands in this subtype were clearly demarcated, regular in contour, and normal in number. Slight marginal irregularity of nodes was found in only 5 of 31 lymphograms and 4 of these were considered normal. Six patients had a regional increase in number of lymph nodes, and this occurred with equal frequency in both normal and abnormal lymphograms.

N.S. – Thirteen of the 31 lymphograms in this subgroup were considered abnormal by commonly used criteria (36). In contrast to L.P., the majority of lymph nodes in all those patients presenting with N.S. showed irregularity of contour of aortic nodes, and small filling defects in the storage patterns of the parenchyma of less than 2 mm in diameter. In N.S., only 8 of 34 patients demonstrated nodes of regular contour and homogeneous filling. Of these, 5 had abnormal mediastinal radiographs and only 3 normal mediastinal appearances. More extensive defects were noted in the node parenchyma of 12 patients with N.S., and a decrease in the normal node number was found in 4. Three patients with N.S. showed even more marked irregularity of the lymph node margin, and a further 2 were considered atypical lymphoma patterns.

M.C. – Because of increase in node size, major marginal irregularities, and larger filling defects, 18 of the 39 lymphograms were considered abnormal. Just over half of these patients had clearly demarcated aortic glands with homogeneous opacification of the parenchyma. Sixteen of the 39 patients showed minor irregularities of contour, and this finding was more marked in a further two lymphograms. Discrete "less than 2 mm" defects in the storage patterns were demonstrated in 15 patients. Larger discrete defects in the node parenchyma were present in 5, and a further 9 showed confluent filling defects. Three atypical lymphoma patterns similar to those seen in 2 of the patients with N.S. occurred in this group.

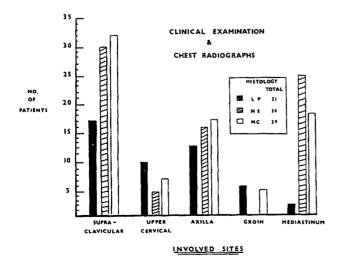
*Pelvic Nodes* – In the pelvic regions, abnormalities of contour and filling defects in the storage patterns of the lymph nodes other than the normal range, were much less common. Seven patients presenting with N.S. showed irregularity of contour, and six of these had filling defects of less than 2 mm size in the parenchymal patterns. In L.P., only one patient showed similar irregularity of contour of the pelvic nodes. Confluent

filling defects were present in three patients of each group presenting with N.S., and L.P. In M.C., no patients were found to have notable irregularity of pelvic node contour, although larger filling defects of the storage patterns were seen in eight patients. The node number was found to be normal in all patients except in three with N.S., who showed a decrease. Thus morphological changes in pelvic nodes have been similar to, but less marked than those described in the aortic chains.

# Lymph Node Areas (Tables 3, 4 and 5)

In those patients presenting with L.P. and M.C., lymphograms could be judged normal or abnormal, and the lymph node areas tabulated accordingly. No equivocal appearances occurred in these groups. In those presenting with N.S., the spectrum of lymph node morphology and size was much more variable. In addition to described criteria for abnormality, many patients were found to have lymph glands of small or normal size, with marginal irregularity and small filling defects in the parenchymal patterns as described in the previous section. Since this study is not concerned with clinical staging per se, but with node morphology including morphometry, when the above findings were present in many nodes, the lymphograms were classified as abnormal. It must be stressed that patients with such findings have thus far been classified as normal in the context of clinical staging (27, 28), but we believe the radiological appearance may be of significance with respect to immune mechanisms and the basic pathogenesis of Hodgkin's Disease (8, 19), and therefore preferred not to classify them as "normal". Figures 3 and 4 illustrate some difficulties in the diagnosis of abnormality in N. S., and the spectrum of morphological changes demonstrated in small nodes by lymphography.

The mean lymph node areas of both aortic regions, for both normal and abnormal lymphograms, in patients presenting with L.P. and M.C. are shown in Table 3. Significant differences in lymph node size are present between normal and abnormal lymphograms. Even on removing those patients with L.P. who actually presented in the groin, these differences in aortic node size persist.



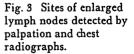


Fig. 4 Female (24 yrs) diagnosed as Hodgkin's Disease with N. S. on left supraclavicular lymph node biopsy. Chest x-ray shows mediastinal mass. Abdominal and pelvic lymphadenograms were interpreted as normal, but note some irregularity of contour and pattern in small nodes. Following laparotomy, focal and subtotal involvement of retroperitoneal lymph nodes and spleen with Hodgkin's Disease of mixed cellularity type was found.

Fig. 5 Female (14 yrs) diagnosed as Hodkin's Disease with N. S. on left supraclavicular lymph node biopsy. Chest x-ray shows a mediastinal mass adjacent to the cardiac shadow. Abdominal and pelvic lymphadenograms were considered normal. Note some irregularity of contour and contrast pattern small nodes. Following laparotomy, a histological diagnosis of chronic lymphadenitis was made in node samples from all areas. No evidence of Hodgkin's Disease was found JAN/66 SEPT/67

Fig. 6 Type 1 Female (44 yrs) from whom biopsy, of a left supraclavicular lymph node showed Hodgkin's Disease with M. C. Sequential lymphograms demonstrate progressive changes in abdominal nodes without alteration in smooth contour or retroperitonealsuperficial topography following presentation with M. C.

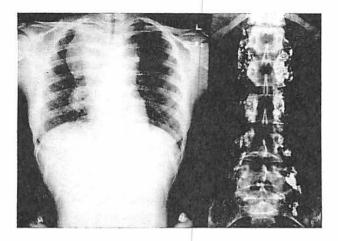


Table 3Mean areas (cm²) of aortic lymphnodes in all patients with L. P. and M. C.

		Right	Aortic	Left Aortic		
		Normal	Ab- normal	Normal	Ab- normal	
L. P.	31	5.68	11.29	7.85	15.22	
M. C.	39	5.97	12.00	7.29	17.56	

Table 4 Mean areas (cm<sup>2</sup>) of aortic lymph nodes of all patients with L. P., and those with M. C. in whom radiographic features were similar to L. P.

		Right.	Aortic	Left Aortic			
		Normal	Ab- normal	Normal	Ab- normal		
L. P.	31	5.68	11.29	7.85	15.22		
M. C.	25	6.20	15.17	7.26	20.60		

Table 5 Mean areas  $(cm^2)$  of a ortic lymph nodes of all patients with N. S., and those with M. C. in whom radiographic features were similar to N. S.

		Right	Aortic	Left Aortic			
	-	Normal	Ab- normal	Normal	Ab- normal		
N. S.	34	8.27	9.02	7.26	10.23		
M. C.	14	5.64	6.28	7.34	10.00		

Fig. 7 Type 2 Female (26 yrs) from whom right supraclavicular lymph node biopsy showed Hodgkin's Disease with M. C. Chest radiograph shows gross mediastinal and contiguous adenopathy. Note numerous small opacified glands with irregularity of contour and parenchymal defects due to H. D. with M. C. at laparotomy.

Since lymph node morphology in 25 of the 39 patients with M.C. was similar to that of L.P., we felt it would be of interest to compare the lymph node areas in this group with those of L.P. (Table 4). While measurements for normal lymphograms remain almost identical, an even greater difference is shown in the node size between the normal and abnormal lymphograms. In 4 of these patients presenting with M.C. mediastinal abnormality was present on the chest radiographs.

Aortic lymph node areas of the remaining 14 patients presenting with M.C. and of 34 patients with N.S. are compared in Table 5. Again normal lymphograms show almost identical areas in the left aortic region. In the right aortic region, the normal lymph node areas in N.S. were higher than in remaining groups but the difference is not significant. A close similarity in lymph node areas of those patients tabulated as abnormal is demonstrated in the left aortic region. All of the 14 patients with M.C. in whom aortic lymph node morphology and size resembled that of N.S., showed abnormal mediastinal radiographs.

Statistical analysis of the left aortic node size in those presenting with L.P., N.S. and each of the two groups of M.C. shown in

Tables 3, 4 and 5 demonstrate a significant difference between those diagnosed as normal and abnormal (P < 0.05). In addition, the difference in the size of abnormal nodes in L.P., and in M.C. with L.P. features, compared with N.S., and M.C. with N.S. features, is significant (T = 2.81 for 102 d.f. P 0.01).

#### Chest Radiographs

More detailed consideration of the presence, size and sites of abnormal soft tissue shadows within the mediastinum in each of the subtypes, confirmed the well-known high incidence of mediastinal involvement in N.S. (22). Eighty-five percent of patients in this subtype on first presentation showed radiographic evidence of mediastinal adenopathy, most marked in the anterior mediastinum, and often extending from the thoracic inlet to the level of the carina. The posterior borders of such abnormal soft tissue shadows, commonly paratracheal and periaortic, were best demonstrated by tomography. The use of transverse axial tomography provided a third dimension in eliciting these findings (15). Subcarinal disease was present in  $28^{0}/_{0}$  of these patients, and hilar adenopathy in  $23^{0}/_{0}$ .

In comparison with N.S., mediastinal abnormality was noted in the initial radiographs of only 2 (6.5%) of the patients with L.P. The radiographic findings in both of these patients differed in no way from many of those with N.S. Neither had subcarinal disease, but one showed hilar adenopathy. Twenty-six percent of patients with N.S. showed opacification of mediastinal lymph nodes following lymphography and this was three times more frequent than in those with L.P.

In the 39 patients with M.C., 19 ( $48.7^{0}/_{0}$ ) chest radiographs showed mediastinal soft tissue masses of similar topography to those in the other subtypes. However, on considering the 14 patients with M.C. in whom retroperitoneal lymph node features were similar to those of N.S. all ( $100^{0}/_{0}$ ) were found to show radiographic evidence of mediastinal adenopathy. This was frequently extensive with occasional involvement of the inferior anterior mediastinum due to parapericardial infiltration. Enlarged hilar nodes were noted in six of these 14 patients.

By contrast, of the remaining 25 patients with M.C., in whom the retroperitoneal lymph node morphology was like L.P., only five showed anterior mediastinal and paratracheal adenopathy. No subcarinal disease was detected in these patients, but hilar lymph node enlargement was noted in three, all of whom showed abnormal aortic nodes indicating widespread disease.

### Summary of Results

The lymphographic features and topography of detected involvement elicited by the diagnostic methods described suggest two recognizable patterns of involvement. In those patients diagnosed as L.P., and in 25 of those with M.C., the lymphograms have shown similar features, namely smooth contour, predominantly homogeneous filling of the parenchyma, and similar size of the opaque images of lymph nodes in both the radio-logically normal and abnormal lymphograms. Detected involvement has generally been in retroperitoneal or superficial lymph node groups and chest radiographs have usually been interpreted as normal. By contrast irregularity of contour and small filling defects

in the parenchyma have been found in a second group consisting of those in whom the initial biopsy was interpreted as N.S., and 14 with M.C. Again in this second group the areas of opacified images of aortic lymph nodes show similar features and the topography of detected adenopathy has been mainly within the mediastinum and contiguous lymph node groups.

#### Discussion

It is of particular interest that following the histological diagnosis of Hodgkin's Disease a combination of clinical and radiographic features suggests that two groups may be identified within the series of patients described. On epidemiological grounds, Mac Mahon (4, 25) for many years has postulated two entities within Hodgkin's Disease. However, on histological grounds this division has not been possible, and individual observers independently evaluating the histological aspect of the Rye classification of Hodgkin's Disease had a level of agreement too low to be scientifically useful (6).

In our series, most of the commonly described lymphographic findings have been demonstrated, and diagnostic accuracy with respect to clinical staging has been similar to that of other centres (31). However, the spectrum of radiographic findings includes decrease and enlargement of lymph nodes as well as changes which, although they may not at present be considered important in management (3) could be of considerable significance with respect to pathogenesis.

Small filling defects in the parenchyma of lymph nodes in man are of similar size and shape to the follicular and pseudo-follicular defects described following lymphography in the experimental animal (32). These are frequently present in reactive hyperplasia regional to sepsis, tumors, and recent surgery (12).

In the present study which is principally concerned with the lymphograms of patients shortly after presentation with Hodgkin's Disease, small, circumscribed, round or oval defects of similar size, in the cortical patterns of lymph glands have been a feature of those with biopsy proven N.S. Such defects have been frequent within the radioopaque images of small nodes of irregular contour. Similar radiographic findings have been detected in the absence of histological Hodgkin's Disease following attempted biopsy of the same nodes (Fig. 4). Lesser degrees of crenation of the contour of small lymph glands which may be an early indicator of stromal abnormality which is not detected in vitro, may also be demonstrated by in vivo radiographic study. Both of the above findings may be obscured in larger glands due to limitations imposed by the oily contrast medium which packs the sinusoids and gives swelling of the nodes (31).

It is of particular relevance to interpretation of lymphograms in this study that a slow rate of introduction of a small quantity of contrast medium in comparison with more rapid infusion of larger amounts, gives increased detail of lymph node parenchyma (8). However, it is now also apparent that the inherent lack of definition on the adenogram displayed by Ultra Fluid Lipiodol in comparison with particulate substances which are not yet available for use in man (7), conceal such findings. Primary radiographic magnification using a small focal spot x-ray tube improves detail and resolution in the adenograms of smaller nodes, but it is anticipated that more sophisticated secondary magnification techniques will yield much more information (10, 26).

Similar radiographic appearances have occurred in patients with follicular lymphoblastic malignant lymphomas in whom no mediastinal abnormality was detected. Such findings have also been noted in patients without malignant disease in whom lymphography was performed because of pyrexia of unknown origin. A single case each of *Waldenstrom's* macroglobulinaemia, and agammaglobulinaemia with hypersplenism, have shown similar radiographic findings in the aortic lymph nodes. Larger circumscribed lacunar defects in the opacified lymph node parenchyma were found by *Wiljasalow* to be significantly more common in N.S. This has also been noted in the present series. Although the smaller "less than 2 mm" in diameter, discrete, radiolucent areas were demonstrated in several patients presenting with L.P., these have been much less common than in those with N.S. Their significance in terms of the pathogenesis of malignant disease and immune mechanism is at present unknown, but may be elicited by lymphographic study during immune reactions (8). It must be stressed that such nonspecific appearance are not yet of diagnostic value in identifying disease involving lymph nodes.

Precise definition of the time at which definite malignant change in a lymph node may be diagnosed histologically presents great difficulties, as does the spectrum of lymphographic appearances ranging from normal to obvious malignant lymphoma. It is suggested that at the present time, both radiolographic findings in the nodes regional to the lower extremities, and histology of node samples at biopsy or laparotomy are complementary in eliciting the poorly understood natural history of malignant lymphomas. It may be anticipated that both may be clarified by this increasing knowledge of the morphology and cytology of lymph nodes during immune reactions and early malignant disease.

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# Thoracic Duct Drainage during Lymphangiography

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#### Summary

In 26 patients lymphangiography was combined with the thoracic duct drainage and with the removal of the contrast medium passing via the thoracic duct. In patients with intact lymph nodes 33.0 per cent and in patients with tumorous involvement of lymph nodes 18.5 per cent of the contrast medium were removed and thus prevented to enter the blood circulation. Thoracic duct drainage prevented the increase in serum GOT which was found in patients submitted to lymphangiography without the thoracic duct drainage. Thoracic duct drainage was supposed to be effective in reducing the risk of oil embolism in lymphangiography.

Lymphangiography has become a useful tool for the diagnosis of obstructive edema, tumorous involvement of lymph nodes, lymphomas and other diseases of the lymphatic system. However, this procedure may lead to side effects which are mostly caused by the passage of the oily contrast medium to the systemic blood circulation. The contrast