Lymphangiograms: Their Diagnostic and Therapeutic Potential

SIDNEY WALLACE, M.D., LAIRD JACKSON, M.D., BURTON SCHAFFER, M.D., JOHN GOULD, M.D., ROY H. GREENING, M.D., ARTHUR WEISS, M.D., and SIMON KRAMER, M.D.

LYMPHANGIOGRAPHY, the radiographic demonstration of the lymphatic system by intralymphatic injection of contrast material, has opened a new field of investigation. Earlier attempts at indirect lymphography were made by injection of radiopaque material into the subcutaneous tissue with uptake in the adjacent nodes (1). Direct injection into large palpable nodes, lymphadenography, was introduced by Carvalho in 1931 (6, 26, 31). Kinmonth in 1955 developed lymphangiography as a method of study of lymphedema of the lower extremities (20). Hreshchyshyn and Sheehan recently modified this approach (13). We have utilized the procedure with only minor variations to study the dynamics of the lymphatic system and the abnormalities in the nodes in various disease states. We have correlated our findings in man with those of animal investigations as summarized by Drinker, Yoffey, and Courtice (8, 29). Our investigation was initiated at Jefferson Medical College Hospital and later extended to include the group at Philadelphia General Hospital.

METHOD

The method of lymphangiography to be described here applies to both the upper and lower extremities. Half a milliliter (0.5 ml.) of a mixture containing equal parts of 0.5 per cent Evans blue dye and 1 per cent procaine hydrochloride is injected intradermally into the interdigital web space between the first and second or fourth and fifth digits of the extremity. The procaine hydrochloride is added to minimize the transitory pain which occurs when the dye is injected alone. The blue dye is selectively absorbed by the lymphatics, making them readily identifiable within fifteen to thirty minutes (Fig. 1). At that time, with aseptic technic, a small skin incision is made proximal to the injection site and a lymphatic conveying the blue dye is identified and isolated. An untied ligature is placed around the vessel proximally to obstruct and distend it temporarily (Fig. 2). A small, narrow-gauge needle (25 to 30 depending on lymphatic size), which has previously been fitted to a polyethylene tube, is then threaded into the vessel and secured in place by a ligature. Ethiodol, an ethyl ester of poppyseed oil containing 37 per cent iodine, is placed in a syringe connected by an adapter to the polyethylene tubing, and low and constant pressure is applied to the syringe by means of a "C-clamp" apparatus, which is manually driven (Fig. 3). The contrast material is thus slowly

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2 National Cancer Institute Fellow.
Fig. 1. Evans blue dye injected in the 1st and 4th interdigital web space. The curvilinear marking on the ulnar aspect of the hand demonstrates a lymphatic.

Fig. 2. Isolation of a lymphatic.

Fig. 3. Apparatus for constant low-pressure injection of contrast material.
forced into the lymphatic system. Best and most extensive visualization is achieved when injections are prolonged over a period of an hour and a half to two hours, at a rate of approximately 7 ml per hour. Undue pressure may cause extravasation of the contrast material into the soft tissues of the extremity. We generally use 5 to 7 ml of radiopaque material in the upper extremity and 10 to 15 ml in the lower extremity, not exceeding a total of 25 ml if both legs are injected. These amounts should be decreased for smaller persons or children in order to avoid forcing the oily material into the general circulation.

Roentgenograms are taken at the completion of the injection for best demonstration of the lymphatic channels. We have found that the patient must remain supine throughout the entire procedure for visualization of the thoracic duct. Injection in the feet will demonstrate the nodes in the inguinal, external iliac, common iliac, and para-aortic areas, as well as the thoracic duct and supraclavicular nodes. The axillary and supraclavicular nodes are seen after injection of the lymphatics of the hand. The contrast material leaves the vessels a few hours after the completion of the injection. The nodes are best seen on the twenty-four-hour films. Normally they may be demonstrable radiographically for approximately four weeks; some abnormal nodes, however, may be visible for as long as four to six months. Roentgenograms for the observation of changes during this period may be obtained without further injection.

CLINICAL MATERIAL

This report presents our results in the lymphangiographic study of 110 patients; 207 extremities were injected: 174 lower and 33 upper extremities. The lesions studied were as follows:

- Carcinoma: 54
- Lymphoma: 28
- Edema: 12
- Infection: 5
- Other: 11

RESULTS AND DISCUSSION

Normally, the lymphatics parallel the venous system throughout the body. In the lower extremities they follow the greater and lesser saphenous veins; in the upper extremities, the basilic and cephalic veins. One lymphatic in each extremity is cannulated and injected, producing adequate visualization of the nodal areas. In the entire lower limb, the lymphatics are of fine caliber (Fig. 4). As they enter the pelvis (Fig. 5, A) and continue through the para-aortic areas, they increase in size (Figs. 5, B, C, D). In the normal limb there is a separate lymphatic drainage for the medial and lateral aspect, with little intercommunication until the inguinal nodes are reached. At the upper level of the sacrum, there is a crossing over to the opposite side. The para-aortic lymphatics drain into the cisterna chyli at about L-2, where this continues on as the thoracic duct (Fig 6). The latter can be seen as it traverses the thoracic cavity up to the left subclavian
vein. Occasionally an anomalous right thoracic duct is demonstrated. Generally some supraclavicular nodes reveal considerable uptake of the contrast medium.

The normal lymphatics of the upper extremities are, as a rule, finer than those of the lower limb (Fig. 7). The lymphatics which follow the basilic vein, traversing the inner aspect of the arm to the axillary nodes, are usually outlined. Here they branch as they continue through the axillary nodes, frequently going through the supraclavicular nodes, finally to reach the subclavian vein (Fig. 8).

Idiopathic Lymphedema: Congenital malformations of the lymphatics are thought to be the primary factor in the production of idiopathic lymphedema. Kinmonth studied 87 cases of idiopathic lymphedema by lymphangiography (21).
He described four primary types of abnormality.  

(a) Hypoplasia (55 per cent of all cases) was the most common finding. Here there were fewer lymphatics, which were usually larger in caliber than in normal patients.  

(b) Dilated or varicose channels (24 per cent) frequently were associated with dermal backflow, which is the demonstration of many small collateral channels in the skin. These dilated vessels often drained into normal lymphatics without evidence of obstruction. Dilatation was occasionally associated with other vascular anomalies.  

(c) Aplasia of the lymphatics was found in 14 per cent of the cases.  

(d) Dermal backflow alone was present in 6 per cent. Kinmonth also postulated that clinical lymphedema may not be manifest in cases of lymphatic abnormality until there is superimposed trauma or infection with concomitant increase in tissue fluid.

One of the 2 cases of idiopathic lymphedema which we studied demonstrates the presence of dilatation and dermal backflow.

Fig. 6. The thoracic duct.

(Fig. 9). Edema did not develop in this patient until the age of twenty-five, approximately six months after an injury to his lower leg. The second patient had idiopathic bilateral lymphedema; none...
of the abnormalities which Kinmonth described were found within the extremities themselves, but dilated channels were seen within the para-aortic area (Fig. 10). The alteration may therefore be in areas which were not demonstrated by Kinmonth.

Acquired Lymphedema and Lymphatic Obstruction: Acquired lymphedema has been studied extensively in animals but has been difficult to produce experimentally. Reichert (1926) divided the tissues of the thigh of a dog with the exception of the major blood vessels and the sciatic nerve, thereby cutting all lymphatics (25). Edema occurred, but subsided following regeneration of the lymphatics by the fourth to eighth day postoperatively. Drinker produced sclerosis of the lymphatics but edema failed to develop until not a single lymphatic trunk could be demonstrated in the extremity. The onset of edema was hastened by preliminary iliac node dissection. It appears, therefore, that marked damage to the lymphatic channels must occur before lymphedema will result.

Of the 3 cases of acquired lymphedema presented, one shows the appearance of dermal backflow as seen in some of the reported idiopathic cases (Fig. 11). This patient received radiation therapy to the leg (left) for a Kaposi's sarcoma. Subsequently edema developed, involving the left leg only. The lymphangiogram is similar to the one reproduced in Figure 9. Two other cases demonstrate lymphatic obstruction with edema due to a neoplasm, with the formation of collateral channels (Figs. 12 and 13). These channels appeared inadequate to handle the increase in tissue fluid. On the other hand, collateral channels may adequately compensate for lymphatic obstruction, in which event no
Idiopathic lymphedema of both lower extremities. Congenital anomalous lymphatics in the retroperitoneal area are shown adjacent to the 4th lumbar vertebra.

Distortion: Changes in the normal distribution of the lymphatic channels may be produced by adjacent masses. This is most frequently seen with pelvic neoplasms. Figure 15 presents a patient who was thought to have pelvic metastasis from carcinoma of the penis.

Normal Lymph Nodes: The lymph nodes are best evaluated by studying roentgenograms made twenty-four hours after injection of the contrast medium. The normal lymph node has a globular or kidney-shaped outline and measures approximately 1.5 cm. in maximum diameter. The margin is frequently interrupted by a slight indentation at the hilus (Fig. 16). The nodal architecture has a homogeneous reticular pattern. The inguinal nodes in adults commonly measure more than 1.5 cm., which we attribute to the frequency of low-grade inflammation in the lower extremity. Our method of injection outlines the skeletal (iliac, para-aortic or vertebral) nodes in contrast to the visceral (mesenteric or mediastinal) nodes. The inguinal, external and common iliac,

edema will occur. This is shown in Figure 14, A with obstruction of lymph flow one year after an inguinal lymph-node dissection for metastatic carcinoma of the penis. In Figure 14, B, there is a similar pattern from pelvic Hodgkin's disease.
para-aortic, and lower supraclavicular nodes are seen following injection of the lymphatics of the lower extremity. The axillary and a portion of the supraclavicular nodes are visualized with upper extremity injection. The contrast material follows the course of normal lymph flow, entering the node through the sinusoids and leaving through the efferent lymphatics at the hilus. According to Collette (7), there are eight to twelve afferent and fewer efferent channels.

Inflammation of the Lymph Nodes: In acute inflammation, as demonstrated by a case of acute thrombophlebitis, there is dilatation of the local lymphatics (Fig. 17). The local nodes are considerably enlarged, but the normal architecture is main-
Fig. 14. Lymphatic obstruction without edema. A. Adequate collateral pathways developing after inguinal node dissection for carcinoma of the penis. B. Extensive collateral lymphatic circulation. Pelvic mass due to Hodgkin's disease obstructing the lymphatic chain.

Fig. 15. Distortion of the left iliac lymphatic chain by a pelvic mass in a patient with carcinoma of the penis.

Fig. 16. Normal lymph node. Multiple fine afferent lymphatics are seen entering the node and larger efferent lymphatics leaving at the hilus. The node has a homogeneous reticular pattern with a well defined margin.

demonstrated by lymphangiography. In metastatic areas there is an increase in the number and size of nodes visualized. A characteristic pattern is produced, which consists of irregular filling defects in the margin of the node, giving it a "moth-eaten" appearance. This is presumably due to embolic carcinomatous metastases. Collette has described such nodes in the pelvis as having enlarged afferent lymphatics; because of the poor filling of the sinusoids, the nodes are of irregular shape, with the defects primarily at the margins, at the site of entrance of the afferent vessels. Fischer demonstrated experimentally in animals that space-taking lesions within the nodes can be clearly visualized. These lesions were simulated by the implantation of polyethylene balls or by the production of sterile abscesses with electrocautery. Intralymphatic injections
Zeidman, Copeland, and Warren (30) injected blue dye and radioactive gold into carcinomatous nodes of rabbits. Radioautography revealed no freely communicating channels between the normal portions of the node and its contained cancer. Even with injection under high pressure with the efferent lymphatics occluded, there was no perfusion through the neoplasm. The carcinoma invades and blocks the lymph spaces; therefore the oil base contrast material will outline only normally functioning lymphoid tissue.

The “moth-eaten” pattern of partial nodal replacement is illustrated by 3 cases.
Fig. 19. Effect of total replacement of nodes by metastatic carcinoma. A. This patient had carcinoma of the prostate with extensive metastatic carcinoma of the retroperitoneal nodes. The nodes are not demonstrated. B. The lymphatics circumvent the totally replaced nodes.

Figure 18, A demonstrates metastatic nodes from carcinoma of the breast. The second case is one of carcinoma of the rectum with metastasis to the para-aortic nodes (Fig. 18, B). The last case shows the effect of complete replacement of the para-aortic nodes in a case of metastasis from a prostatic carcinoma (Fig. 19). Although the enlarged nodes cannot themselves be visualized, the deviated lymphatics give away their presence. With metastatic nodal involvement there is an increase in the number of lymphatics and nodes seen, which may be due to the visualization of different pathways or new node formation.

**Lymphoma:** In lymphomatous diseases, the lymph nodes are enlarged and have a foamy or lacy pattern which produces an almost ghost-like appearance. In contrast to invasion by metastatic carcinoma, the important finding is preservation of the outer margin of the node. This is consistent with the pathologic change in lymphomatous disease, which is initiated within the node and spreads diffusely through it. Our experience suggests that some lymphomatous diseases have characteristic patterns. Nodes involved with lymphosarcoma, as seen in Figures 20, A and B, are enlarged, the margins are maintained, and there is a foamy or lacy pattern. In Hodgkin's disease, as shown in Figure 20, C, the nodes are large, with the borders preserved but scattered areas of moth-eaten replacement are present within the node. In 2 patients with chronic lymphatic leukemia, an identical pattern was seen, with enlarged nodes having basically a lacy architecture, continuous margins, and areas
Fig. 20. Lymphomatous involvement of lymph nodes. These nodes show a foamy internal architecture, with preservation of the nodal margins. A. Lymphosarcoma, early manifestations. B. Lymphosarcoma, late stage. C. Hodgkin's granuloma. D. Chronic lymphocytic leukemia.

of increased collections of opaque medium (Fig. 20, D). These basic criteria are employed in the evaluation of the patient studied by lymphangiography.

APPLICATIONS AND COMPLICATIONS

Lymphangiography is a practical method of radiographic demonstration of the lymphatic system. It can be utilized as a diagnostic tool and as a therapeutic aid which has definite practical clinical applications. The procedure requires a minimum of surgical proficiency, so that under the usual circumstances the technical aspects are accomplished in approximately half an hour.

Diagnosis: In cases of lymphedema, localized abnormalities of the lymphatic system can be demonstrated. Perhaps surgical approach to these congenital anomalies may be of value in correction of "idiopathic lymphedema."

Postoperative edema following radical mastectomy is frequently a distressing
problem. Several such patients have been studied in this group. In one, the lymphatics were normal in number but decreased in caliber (Fig. 21). This finding differs from that of Kinmonth, who found the vessels near-normal in caliber but somewhat tortuous and with a tendency toward increased collateral flow. In a recent investigation by Smedal and Evans (27), by means of venography, several patients were found to have thrombophlebitis as the prime causative factor. In an attempt at a better study of postmastectomy edema, we are now using combined venography and lymphangiography. It is of interest that in a case of chronic thrombophlebitis of the lower extremity the
lymphatics were decreased in number and
caliber somewhat as in post-mastectomy
edema.

Diagnostically, lymphangiography can
be best applied to the patient with mali-
gnant diseases. Demonstration of mete-
static carcinoma of the lymph nodes by this technic may furnish information of critical value in the presence of unsuspected metastatic disease, which may alter the therapeutic approach. Even in an accessible area such as the axilla, metastatic carcinoma may be present at the apex, and therefore out of reach of the palpating fingers. Figure 22, A represents a patient with an extensive lesion of the breast with two large firm axillary nodes. A lymphangiogram revealed multiple involved nodes. Note the worm-eaten appearance. A radical mastectomy was performed. All the nodes removed contained metastatic carcinoma. The areas visualized are residual functioning tissue. The majority of the nodes were totally replaced and showed no uptake of contrast material. Figure 22, B shows the dissected nodes. Those which were visualized were completely removed, as was shown in a postoperative chest film.

Lymphomas can also be readily shown by this technic. The lymphangiograms will frequently reveal diffuse malignant involvement where only local disease is manifest clinically. This was demonstrated by a patient with Hodgkin's granuloma believed to be localized in the supraclavicular area. Examination disclosed extensive disease in the retroperitoneal region. The nodes were typical of Hodgkin's disease, with a well defined outer margin and spotty replacement within (Fig. 23). Figure 24, A shows a reticulum-cell sarcoma producing distortion of the ureter. Fig. 24, B reveals displacement of the kidney by nodes involved by chronic lymphatic leukemia.

In selected cases the exact location of tumor-producing symptoms was depicted. This has led to more specific therapy. In one patient, for example, who was known to have lymphosarcoma, urinary obstruction suddenly developed. Intravenous urography was inconclusive because of inadequate concentration of the contrast medium. The lymphangiogram depicted enlarged involved nodes in close proximity to the ureters. Radiation therapy to this area resulted in the relief of obstruction. In another case, a patient with a history of laryngectomy for carcinoma ten years previously complained of sudden back pain. No bony involvement, however, could be demonstrated. To our surprise the lymphangiogram revealed local involvement of retroperitoneal nodes at the level of the symptoms. This proved to be Hodgkin's disease, and subsequent irradiation brought about relief.
Fig 25. Lymphangiography as a guide to retroperitoneal node dissection.  A. Preoperative films of the abdomen, both anteroposterior and lateral, in a patient with teratocarcinoma of the left testicle. Note the suspicious nodes to the left of the 2nd lumbar vertebra.  B. Postoperative roentgenograms reveal residual nodes. The questionably involved nodes are still present.

**Therapeutic Applications:** Lymphangiography can be a valuable aid to the surgeon. This procedure performed prior to lymph-node dissection can be used to give the surgeon a more exact visual picture of the location and status of the nodes.
Fig. 26. Lymphangiography as a surgical and radiotherapeutic guide. A. The preoperative examination of a patient with teratocarcinoma of the testicle. B. Postoperative roentgenogram showing many residual nodes. C. Post-radiotherapy film. The nodes are markedly decreased in size but maintain the same configuration. The change is due to the effect of treatment rather than the loss of contrast material from the node.

Fig. 27. Evaluation of the effect of radiotherapy. A. The axillary nodes show lymphosarcoma. B. Eleven days following the initiation of radiotherapy.
Fig. 28. Effect of chemotherapy. A. Lymphosarcoma of retroperitoneal and pelvic nodes. B. One week after initiation of cyclophosphamide therapy. C. Six months follow-up. The nodes are smaller, well visualized, and have the same configuration.

An example of this is seen in Figures 25, A and B, which show pre- and postoperative films of the retroperitoneal nodes of a patient with teratocarcinoma of the left testicle. Even though an apparently complete retroperitoneal node dissection was performed, the postoperative film revealed one node showing changes suggestive of involvement, which was left behind. Roentgenograms taken in the operating room may serve as a guide to complete removal of the nodes.

Lymphangiography can be utilized to great advantage by the radiotherapist, particularly in the more accurate placement of treatment portals. Our roentgenograms of the axillary nodes have demonstrated that some of these may lie at a distance below the clavicle and may therefore be missed by postmastectomy irradiation. Portal films can be more accurately centered over the proper area.

Visualization of the retroperitoneal nodes is a most helpful guide to the radiotherapist in the treatment of testicular tumor metastases. Crossing-over commonly takes place at the first sacral area and both para-
aortic chains must be included down to this level. Figure 26, A is the preoperative picture; Figure 26, B postoperative, and Figure 26, C post-radiotherapy.

Therapeutic efficacy can also be more exactly determined because of the prolonged presence of the contrast medium.

A patient with far advanced lymphosarcoma received radiotherapy to the axilla. Eleven days after the initiation of treatment, a follow-up film dramatically revealed the regression of the nodes (Figs. 27, A and B).

The latter use also applies to chemotherapy of disseminated malignant disease. Not only does it give the chemotherapist a guide to the effect of treatment in the individual patient, but it also gives him another practical parameter for objective evaluation of his therapeutic agents. This is demonstrated beautifully by a case of lymphosarcoma (Fig. 28, A) treated by intralymphatic and oral cyclophosphamide. Films taken in one week showed considerable regression (Fig. 28, B). Follow-up roentgenograms after six months once again show the nodes to be much smaller but with the same general configuration (Fig. 28, C). With exacerbation of the disease, the nodes will once again enlarge and revert to the previous status.

Intralymphatic injection of chemotherapeutic agents following the demonstration of nodes involved by neoplasm has been attempted. Thus far only a few patients have been treated, without very rewarding results.

Complications: In performing lymphangiography on 207 extremities in 110 patients, we have encountered infrequent and minor complications. Two of our patients experienced a transient lymphangitis, which we assumed to be chemical in nature. This rapidly responded to local therapy. Local wound inflammation has occurred occasionally and led to frank wound infection in 3 instances. Histologic examination of nodes removed at surgery following lymphangiography has shown lipoid material producing a foreign-body reaction, a lipogranuloma (Fig. 29). The significance of this observation is not known at present. In a repeat study after ten months we have not demonstrated any nodal changes which could be ascribed to the previous study. There is always the possibility of the contrast material enter-
ing the venous circulation either too rapidly or in an excessive quantity. This can lead to fine pulmonary embolization, and we have observed this in a few patients (Fig. 30). In 6 of these a febrile response developed which was self-limited and subsided within three days without significant morbidity. The contrast medium itself has always cleared completely within a week. We attempt to avoid this complication by limiting the quantity of injected material in each patient. A theoretically possible complication is further spread of tumor emboli as a result of lymphangiography. This phenomenon is difficult to investigate. The work of Zeidman et al. (30), however, suggests that it is a remote risk. Lastly, one must always keep in mind the possibility of iodine sensitivity.

**SUMMARY**

By a modification of Kinmonth’s method of intralymphatic injection, the lymphatics and nodes of the extremities have been demonstrated, including the pelvic, paraaortic, axillary, and supraclavicular areas, as well as the thoracic duct.

In lymphedema the findings vary from an increase to an almost complete absence of channels. Extensive collateral pathways in the face of obstruction to lymph flow have been shown.

Normal nodes exhibit a homogeneous reticular pattern. In lymphadenitis, the nodes are larger but normal in architecture; in lymphomas there are enlarged, lacy, ghost-like nodes; in carcinoma the nodes have a moth-eaten appearance.

Lymphangiography can be used to determine the general type and extent of disease processes; as a guide to lymph node dissection; in radiation therapy for portal placement; and in both radiotherapy and chemotherapy to assess the response to treatment.

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Department of Radiology
Jefferson Medical College Hospital
Philadelphia 7, Penna.

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SUMMARIO IN INTERLINGUA

Lymphangiogrammas: Lor Potential Diagnostic e Therapeutic

Per medio de un modification del metodo de Kinmonth de injectiones intralymphatic, le vasos lymphatic e le nodos esseva demonstrate in le extremitates e etiam in le areas pelvic, para-aortic, axillari, e supraclavicular, si ben como le ducto thoracic. In lymphedema, le constatationes varia ab un augmento usque ad un quasi complete absentia de canales. Extense circuitos collateral in le presentia de obstruction del fluxo lymphatic esseva demonstrate.