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Lymph nodes and vessels in primary lymphoedema

Their relative importance in aetiology

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Summary

The classification of lymphoedemas is reviewed and the various primary lymphoedemas distinguished from the secondary. The early lymphographic studies of primary lymphoedemas (many of which arise from genetic factors) probably laid undue emphasis on changes in the lymphatic vessels. Oil contrast media in later use in lymphography have given much information on changes in the nodes. In 89% of patients reviewed both nodes and vessels were diseased and in the majority the changes were worse in the nodes. This suggests that in many patients with primary hypoplastic lymphoedema the pathological process has arisen first in the nodes.

Introduction

The early lymphographic investigation of the lymph system in patients with primary lymphoedema was done with water-soluble contrast media, which gave good information about the vessels but relatively little on the state of the regional nodes and even less on the more proximal and central nodes. This focused attention particularly on the vessels, and the first classification of the state of the lymph system in primary lymphoedema was based on their appearance in lymphangiograms[1].

Oil contrast media, introduced by Brunn and Engeset[2], have allowed much better study of the nodes and central vessels, particularly from radiographs made hours, days, and even weeks after the initial injection. It has been possible to study the rate of passage of the medium through regional and trunk nodes ('transit time'). This has often given evidence of abnormality even in the absence of the more obvious changes in number, shape, and density of the nodes[3].

The impression has grown that in many patients the abnormality lies often more in the nodes than in the vessels and indeed that the initial pathological change might lie there and that the vessel changes might be purely secondary, due to stasis or distension. It was therefore decided to review the lymphograms of a group of patients with primary lymphoedema of the lower limb investigated and treated in the surgical clinical professorial unit at St Thomas's Hospital.

Classification of lymphoedemas

The patients reviewed all had primary lymphoedema. It is helpful to recall the modern classification of lymphoedemas to understand their place. The first main division is between the secondary lymphoedemas and the primary.

Secondary lymphoedemas are those in which the lymph system has been damaged by some well-recognized pathological process, examples being: extensive malignant disease (either primary or metastatic), filariasis, surgical excision, high doses of radiation, and other causes.

Primary lymphoedemas arise, in patients in whom no such pathological process is present, as a result of changes in the fluid-conducting components of the lymph system. The changes may occur either in the lymph vessels or in the nodes, or in both. All lymph from the periphery appears to pass through nodes. We do not recall ever seeing lymph vessels on lymphograms which completely bypassed all nodes. Free conduction through the nodal areas is therefore just as important in the avoidance of oedema as conduction through the vessels.

Classification of primary lymphoedemas

Primary lymphoedemas may be classified in several ways: (*a*) very simply, by age at onset (congenita, praecox, tarda); (*b*) by lymphographic findings (aplasia, hypoplasia, hyperplasia); or (*c*) on a clinicopathological basis into separate disease entities.

Six of the latter which were recognized in 1972[3] were:

1) Lymphoedema with unilateral hyperplasia of lymph vessels ('megalymphatics').
2) Lymphoedema with bilateral hyperplasia. These cases often appear to be due to a congenital defect of the thoracic duct, sometimes associated with congenital cardiac defects[4].
3) Lymphoedema with gonad dysgenesis (Turner's and other syndromes).
4) Lymphoedema with pes cavus.
5) Milroy's disease (congenital familial lymphoedema).
6) Primary hypoplastic lymphoedema.

The last is numerically the largest group. There is a family history in some 25% of cases and the condition is more common in females. It may be broken down into further disease entities in future as knowledge advances. It is from this last group that the patients in this review were drawn.

Present study

The present study was undertaken to examine further the relative importance of changes in the vessels and nodes. The clinical case histories and lymphographic studies of patients investigated and treated in the surgical professorial unit at St Thomas's Hospital during a 2-year period from 1973 to 1975 were reviewed. Attention was focused on patients suffering from primary hypoplastic lymphoedema. No patients suffering from other lymphatic diseases such as congenital megalymphatics, Milroy's disease, or lymphoedema with gonad dysgenesis were included.

Bipedal lymphography was performed by the standard techniques[3] of dissection and injection of lymph vessels on the dorsum of the foot following preliminary visualization with interdigital injection of patent blue violet. In cases in which no suitable vessel could be

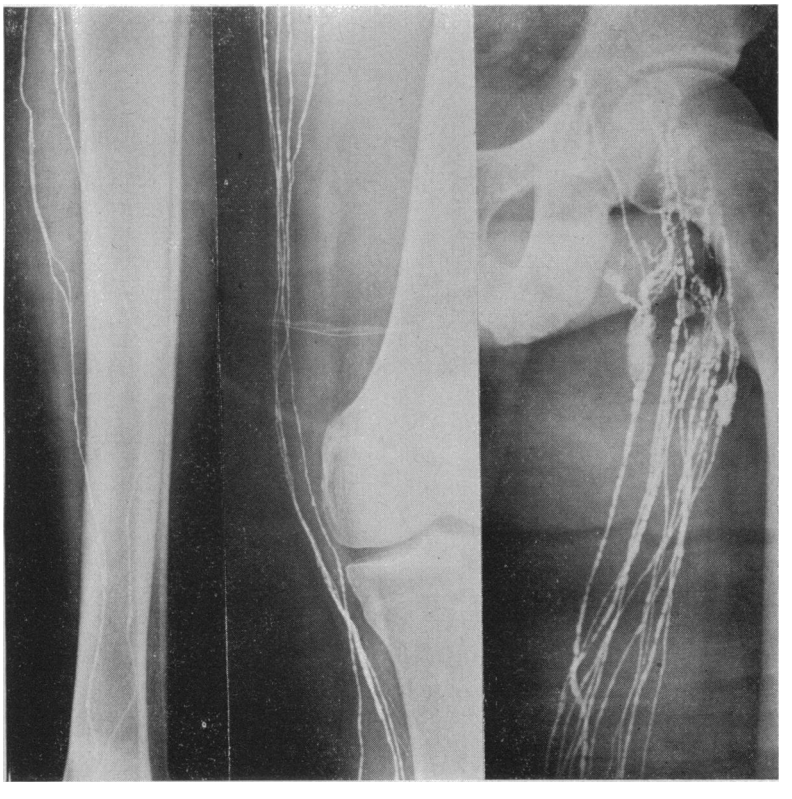


FIG. 1 *Normal lymphangiograms of leg and thigh. Only 3 vessels fill in the lower leg. Some 5–15 vessels may be seen in the groin (in this case 9 have filled). Note oval swellings, corresponding to valve ampullae, and early filling of nodes. (Man aged 47 under investigation for possible abdominal lymphoma.)*

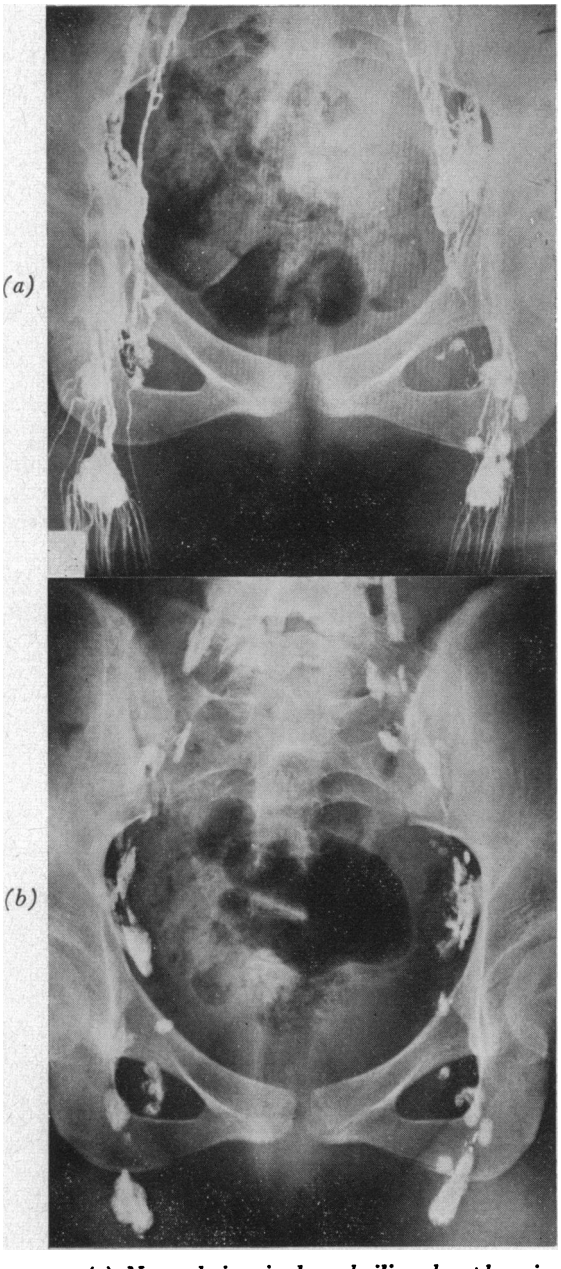


FIG. 2 *(a) Normal inguinal and iliac lymphangiograms with early filling stage of nodes. (b) Normal pelvic lymphadenograms 24 hours later. Lipiodol has cleared from the vessels. Nodes of normal granularity and morphology. (Woman aged 18 under medical investigation for symptoms later diagnosed as functional.)*

found on the foot for injection of iodized oil (Lipiodol) a search was made in the groin after further injections of patent blue violet at a number of points at knee and lower thigh level. Afferent lymph vessels near the superficial inguinal nodes were then sought through a short transverse incision and injected with Lipiodol.

The standard volume of Lipiodol Ultra-Fluid injected in each limb was 6–7 ml for an adult. It was thought when originally planning this study that limbs into which smaller volumes had been injected might need to be excluded on the grounds that the available lymph passages might be incompletely filled and therefore not provide a fair comparison. In the event it was evident from the radiographs that quite small volumes, often as little as 2 ml, were quite sufficient to fill completely all lymph vessels and nodes available to be filled.

Limbs in which lymph vessels were absent (aplasia) or too small to inject (very severe hypoplasia) were excluded from the review as no judgment could be made on the relative roles of nodes and vessels.

All patients included had primary hypoplastic lymphoedema of the lower limb (that is, Group 6 above). There were 55 patients (11 male, 44 female), ranging in age from 10 to 59 years. Patients were included only if sufficient Lipiodol had been injected to outline fully the available lymph vessels and nodes. Assessment was made on lymphographs of the affected limb or, if both limbs were involved, of both. The statistics therefore refer to numbers of patients rather than of limbs.

Results

It will be seen from the table that the patients fell into three groups.

1) Both nodes and vessels affected Most of the patients (49/55; 89%) fell into this group, in which both nodes and vessels showed evidence of disease in the lymphograms. In 30

Bipedal lymphography in 55 patients with primary hypoplastic lymphoedema.

Both lymph nodes and vessels diseased	49	(89%)
worse in nodes 30		
worse in vessels 9		
equal 10		
Lymph vessels only diseased	5	(9%)
Lymph nodes only diseased	1	(2%)
	55	

patients—more than half of the entire series—the nodes were much more seriously affected than the vessels. Among them were 17 patients showing the changes of proximal hypoplasia with distal distension; in these the nodes were absent or small, misshapen, and varying in density. The changes were often extensive, the inguinal, iliac, and lumbar nodes being involved. The lymph vessels in the limbs showed changes similar to those seen in secondary lymphoedema such as might follow radical surgical excision of regional nodes. A huge distended network of vessels was seen in the limb, with dye running from dilated deep vessels in a retrograde fashion into the smaller collectors and plexuses of the skin. This 'dermal backflow' was also evident to the naked eye when the patent blue dye was injected during the preliminary visual stage of lymphography.

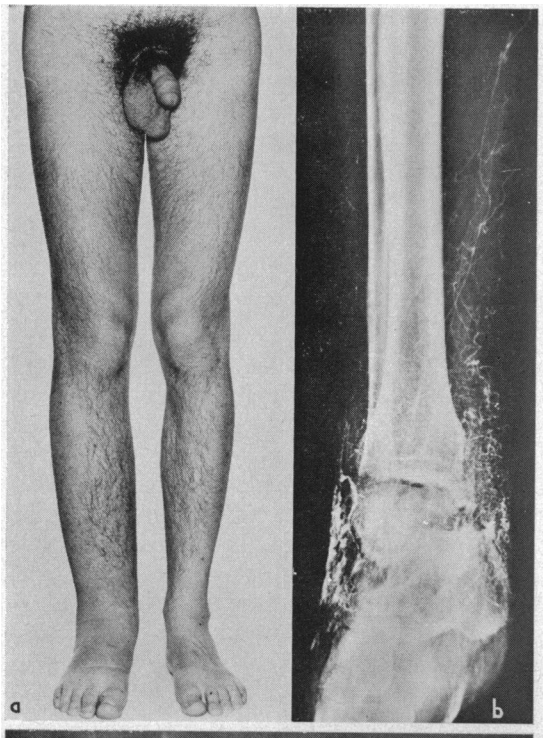
The ease with which the Lipiodol passed through the regional nodes varied. In some cases it reached and filled the first nodes in appreciable numbers, but there was evidence of obstruction in them manifested by retrograde filling of other afferent vessels and also of collateral circulation past the nodes. The efferent vessels and subsequent nodes were much more poorly filled, final delineation of the pelvic and lumbar pathways sometimes taking several days instead of hours to complete. The slow passage through the nodes and the whole picture pointed strongly to a fault which had started in the nodes and produced obstruction of a relatively normal tree of lymph vessels in the limb. These patients often had severe and extensive oedema, with the whole limb including the thigh and sometimes also the genitalia, lower abdominal wall, and buttock involved. The patient illustrated in Figure 3 showed many of the features of proximal hypoplasia with distal distension.

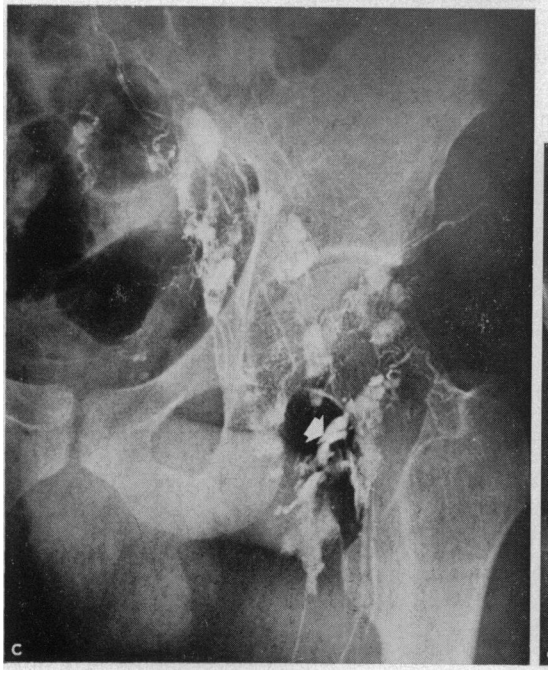
At the opposite end of the spectrum, among those with the disease worse in the vessels than in the nodes, were patients, often females with mild peripheral oedema, in whom the lymphadenograms were relatively normal but the peripheral vessels severely hypoplastic in number and size. An extreme example could be a solitary vessel found on the dorsum of the foot, small and cannulated with difficulty and running without any of the normal multiplication to one of the inguinal nodes. From there on the nodes and efferent vessels showed only minor abnormalities and with normal transit time of the dye through the pelvic pathways. There were 9 of these patients in whom the vessels were manifestly more diseased than the nodes (Fig. 4).

In 10 patients the degree of involvement appeared to be equally distributed between nodes and vessels.

2) Lymph vessels only affected Five patients, women ranging from 20 to 49 years of age with peripheral oedema, had hypoplastic vessels but nodes which fell within normal limits, including normal transit time of the dye through the pathways of the pelvis and abdomen to the thoracic duct. Their lymphadenograms were examined carefully, and although minor imperfections and irregularities were seen, they were considered to be no worse than might be seen in a similar range of normal subjects of their age and sex in whom fibrofatty deposits and other small defects might cause similar appearances.

3) Nodes only diseased The one patient in whom the nodes only appeared to be diseased was somewhat unusual. This was a woman aged 22 with a 4-year history of swollen ankles and legs. Her mother had also suffered from swollen ankles. Her serum protein concentration was at the lower limit of normality and there was found to be excessive loss of protein in the stools, possibly due to mesenteric lymph obstruction[5]. Lymphography showed numerous well-filled vessels in the lower limbs but obstruction and collateral circulation, with ectopic nodes filling in the lumbar region and region of the cisterna chyli. The transit time was abnormally slow through the lumbar region. There were no defects in the vessels other than increased filling and collateral formation. The nodes appeared smaller than normal. This also suggested an obstructive factor in the nodes in the lumbar region. It was probably responsible both for intestinal protein loss and for the oedema of the legs. The latter may have been aggravated by the low level of plasma proteins.





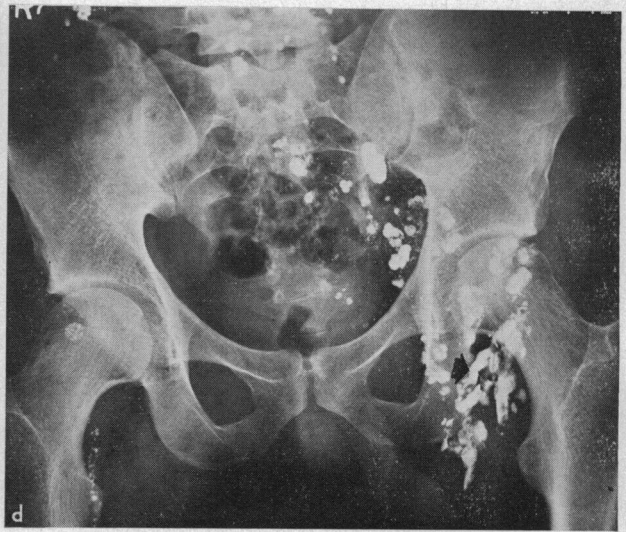


FIG. 3 *(a) Lymphoedema due to major hypoplastic changes originating in the nodes in the trunk in man aged 24. Swelling of right leg and thigh of spontaneous origin for 2 years and right hydrocele of 10 years' duration. Left leg remains clinically normal despite nodal changes in lymphograms. (b) Obstructive appearance shown after injection in lymphatic on right foot. Retrograde flow into tortuous lymphatics reaching dermal plexus of foot and ankle. A single small irregular lymphatic runs upwards to knee. (c) Early node-filling phase of lymphogram on patient's left (good) side. There are 4 afferents in the groin (normal 5 or more). Nodes are irregular and extravasation is starting (arrow). The efferent vessels are small and tortuous. Also collateral formation and retrograde flow both medially and laterally (cf Fig. 2). There is as yet little obliteration of vessels on this side. (Despite the X-ray changes the patient has remained free of oedema on this side, presumably through adequacy of the collateral circulation.) (d) Lymphadenograms (24-h films) show almost no nodes outlined on the right. There is a single node in line with the femoral head and an ectopic node near the iliac crest. On the left side there is extensive disease of nodes (cf Fig. 2). Many are smaller and denser than normal and lie out of the normal position. Inguinal nodes are numerous, small, and round. There are areas of extravasation of dye, not normally seen (arrow).*

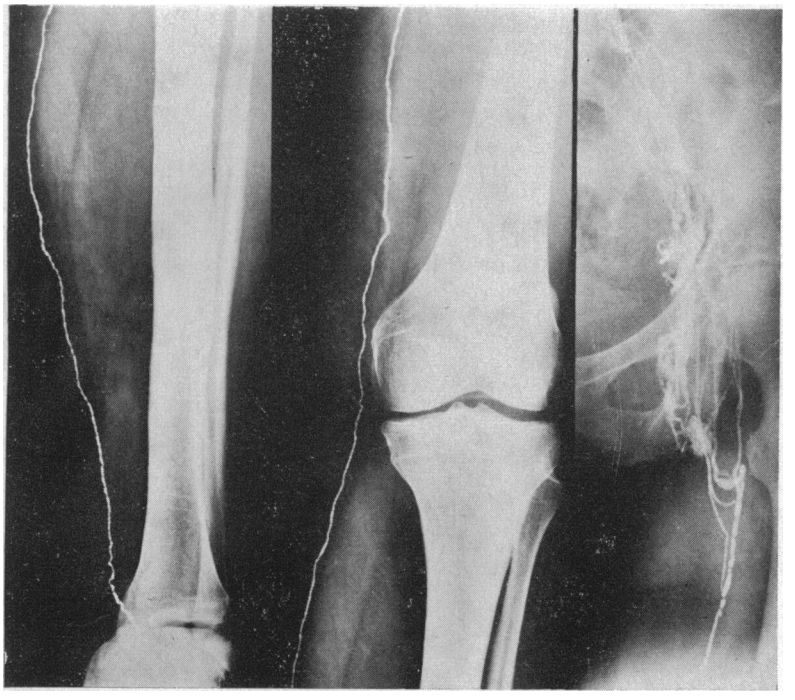


FIG. 4 *Lymphangiogram of patient in whom the hypoplastic disease process appeared to originate in and be almost confined to the vessels. Only one solitary lymph vessel is filled, but the pathways from the inguinal nodes upwards appear normal. Lymphadenograms showed minimal abnormality. (Woman aged 43, oedema of both feet and ankles, left for 1 year, right for 8 years. Vessels on the right were too hypoplastic to inject.)*

Discussion

In assessing the relative importance of disease of the nodes and the lymphatics in the genesis of hypoplastic lymphoedema the relationship between the two under other circumstances must be considered If the nodes are removed what will happen to the lymphatics that remain? Or alternatively, if the afferent lymphatics are removed or destroyed or cease to function what will happen to the nodes to which they once brought lymph? Will they remain unchanged or perhaps atrophy?

Much has been learnt to answer the first question from lymphography of limbs after regional node dissections. We have found the typical distended obstructive picture in earlier cases, but as the years pass changes occur and the lymphatics often atrophy and may disappear completely. This has been found on repeated lymphography in both upper and lower limbs. Danese and Howard[6] described this disappearance or die-back of lymphatics in postmastectomy oedema and Jackson[7] described it in the lower limb. Patients with primary lymphoedema due to changes occurring first in the regional nodes might ultimately in the same way show hypoplastic changes in vessels as well. The process would tend to increase the number of patients with apparent disease in both nodes and vessels.

The answer to the second question is more difficult. That failure of afferent lymphatics may leave the nodes relatively unchanged was suggested by lymphography in a middle-aged man whose leg had been amputated through the thigh in childhood. The regional nodes were found to be surprisingly unchanged despite the ablation of most of the afferent lymph supply. Such immunity to change in the nodes suggests that the figure of 5 patients with 'vessels only diseased' is more representative of the true incidence of the site of the initial pathological change than the statistics for the group in which nodes and vessels are both affected. The latter group probably contains many cases in which the disease was initially in nodes.

Conclusions

1) Early studies of patients with primary lymphoedema suggested that the pathological process or inherent defect in the lymph pathways lay chiefly in the lymph vessels.

2) Later studies giving more information on the nodes suggest that nodal hypoplasia is often extensive and important in the genesis of

lymphoedema.

3) Of this series of 55 patients, 49 showed disease affecting both nodes and vessels. In 30 it was considered worse in the nodes than in the vessels.

4) The figure for 'nodes worse' may be larger than is apparent owing to the natural tendency for peripheral vessels to atrophy after node ablation.

5) The figure for 'vessels only diseased', although small, is probably representative of a small number of cases in which the hypoplastic defect is truly peripheral.

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