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Fibrosis in the lymph nodes in primary lymphoedema

Histological and clinical studies in 74 patients with lower-limb oedema

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Summary

There are many different clinical and lymphographic groups of patients with primary lymphoedema. Improved lymphographic techniques have emphasised the importance of changes in the nodes as well as in the lymph vessels.

A systematic histological study has been made of nodes removed during therapeutic operations or investigations on patients with primary lymphoedema. Many nodes showed a marked fibrotic process. This, in its distribution in the node and its histological appearance, was quite different from that which might have arisen from attacks of infection and inflammation. The majority of patients had no clinical history of such attacks. It may be regarded as primary fibrosis *in the nodes. Associated clinical features suggest strong genetic or familial factors in its aetiology. Many of the changes found in the lymph vessels may follow obstructive effects from fibrosis in the nodes.*

The histological findings have been related to the clinical and lymphographic features in different types of primary lymphoedema. The degree of fibrosis and its distribution have important bearings on the prognosis, clinical course, and treatment of the patient.

Introduction

Continuous improvement in lymphographic techniques, with more detailed studies of the pathways in the trunk to include the nodes and the thoracic duct, has shown the great importance of the lymph nodes as opposed to the peripheral vessels in lymphoedema *(1)*.

For many years we hesitated to carry out biopsy on nodes in patients with primary lymphoedema, fearing that the circulation might be further damaged. However, in many lymphograms there were features which suggested that nodes might be actually the seat of obstruction. Good afferent lymph vessels might be seen coming right up to the node, with poor exit from it and with evidence of collateral circulation around it. One member of our team actually suggested that if such nodes could be excised, preserving as far as possible the vessels, the return of lymph might be improved. This was done in a few cases but without obvious reduction in the oedema. On the other hand the oedema was never aggravated and it was therefore thought safe to excise, in the same manner, selected nodes from other patients, as valuable information about the underlying pathology might be gleaned by microscopy. This has been done in a series of patients during the past 2 years.

In many nodes a dense and spectacular fibrosis was found. In other nodes there were lesser degrees of fibrosis. The peripheral lymph vessels had been studied by biopsy of small segments (chiefly from the feet) in our patients with lymphoedema for 15 years. These studies have been continued and the findings related to those in the nodes *(2,3)* (Kinmonth JB, Boggon RP, unpublished observations). The new histological data have been related to the lymphographic and clinical features of patients to assess further this

role of the fibrosis and the relative importance of node and vessel disease.

This paper describes the results in different types of primary lymphoedema. They have an important bearing on the prognosis and treatment in the various groups of patients.

Patients

Seventy-four patients with primary lymphoedema of the lower limbs have been studied. Fifty-two were female and 22 male. The median age of onset of the lymphoedema was 15 years (range congenital–74 years). Five had congenital lymphoedema (2 of them with Milroy's disease (familial congenital lymphoedema)), 60 lymphoedema praecox, and 9 lymphoedema tarda (onset after the age of 35). These patients were a selected group in that it was important to obtain an adequate number of lymph-node biopsy specimens from all forms of primary lymphoedema. Consequently there is a disproportionately large number of patients with hyperplastic lymphatics in the series. Apart from this slight disproportion the distribution is very like that found in clinical practice. After a clinical assessment, taking particular note of the duration and severity of the lymphoedema, familial history of the disease, any precipitating cause for the oedema, and episodes of cellulitis, each patient underwent bilateral lymphography.

Methods

LYMPHOGRAPHY

About 0.1 ml of 11% patent blue violet was injected subcutaneously into each interdigital cleft in order to show a lymphatic on the dorsum of the foot; this was then cannulated and injected with Lipiodol Ultra-Fluid (iodised oil fluid injection) in the usual manner *(1)*. In some patients there were no patent lymphatics in the foot and a direct inguinal-node injection was performed with Lipiodol.

The lymphograms were classified as follows:

1) Hypoplasia, distal (22 patients): lymph vessels too small or too few in limb.
2) Hypoplasia, proximal (19 patients): vessels and nodes too small or too few in groin and pelvis. Vessels in limb numerous, tortuous, and dilated (that is, obstructed and distended).
3) Hypoplasia, distal and proximal (19 patients): a combination of (1) and (2) (that is, vessels and nodes too small and few in limb and pelvis).
4) Hyperplasia: *(a)* Bilateral (11 patients): numerous tortuous lymphatics in both limbs with many large nodes in groins and trunk. Non-filling or distorted thoracic duct.

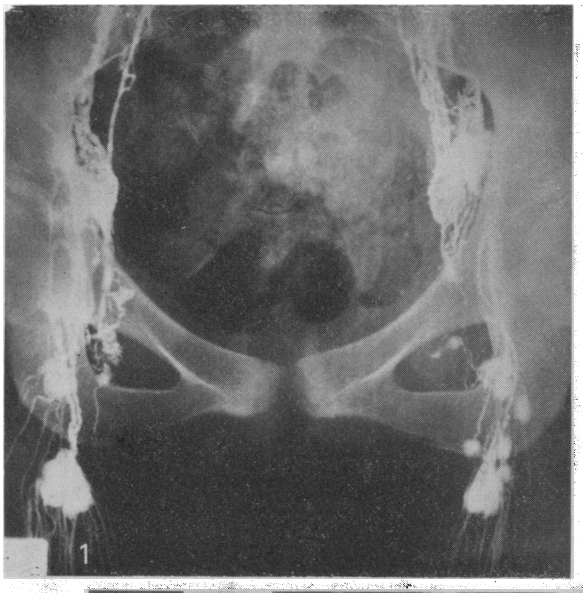
   (b) Megalymphatics (3 patients): many large, tortuous, varicose lymphatics in limb and trunk. Nodes diffuse, scattered, often numerous. Almost always unilateral.

This classification was made on the *lymphangiograms*—that is, the radiographs taken soon after injection when the lymph vessels are filled and the nodes in the early filling stage. Our previous study *(4)* on nodes and vessels included the lymphadenograms—that is, the delayed radiographs at 24 hours or later when the contrast medium might be expected to have left the vessels, revealing the state of the nodes.

Classification by lymphangiogram has the effect of simplifying the number of groups; there would otherwise have been a number of subgroups, making numerical presentation of the results confused. The lymphadenograms are more sensitive than the lymphangiograms in detecting lesser degrees of abnormality. It must be realised, therefore, that there is probably a less clearcut distinction between the groups than there might seem to be from the numerical data obtained.

Examples of a normal lymphogram and lymphograms from some of the groups are shown in Figures 1–4. (A much more detailed description of these groups with illustrations may be found elsewhere *(1)*.)

No patients in this series were classified as having aplasia. Patients with aplasia *(1)* are those in whom no formed lymph vessels, nor any structure resembling even a remnant of a lymph vessel, can be found in the area explored. Some patients are found to have aplasia in one area and hypoplasia in others. Such cases have been classified as hypoplasia. There were no cases of pure aplasia in this series. The question of aplasia will be discussed more fully below.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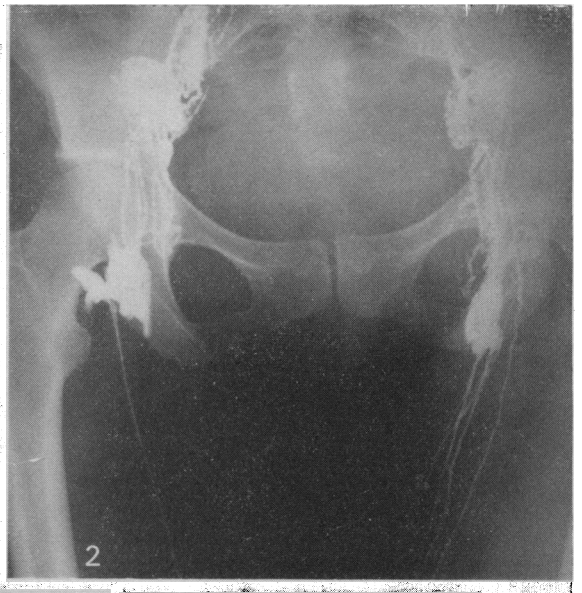
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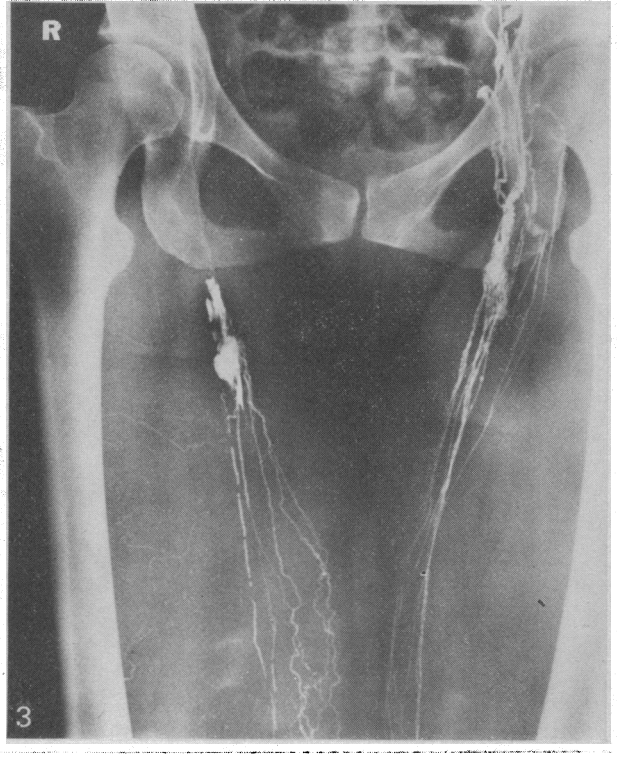
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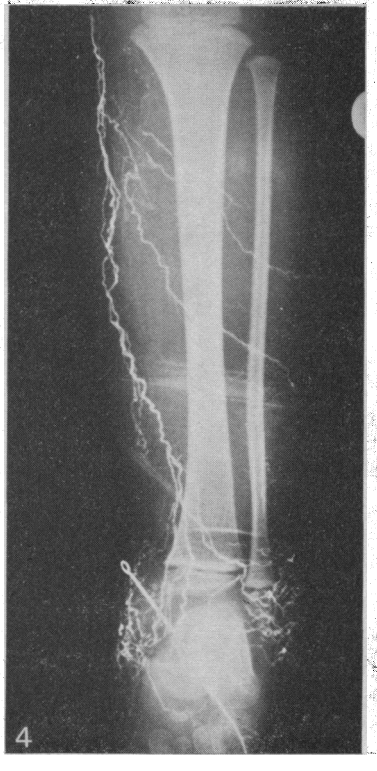
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LYMPH-NODE HISTOLOGY

After lymphography a superficial inguinal lymph node in each patient was removed for histological examination and the site marked with Ligaclips. Our practice was to try to obtain a node from the centre of the inguinal group on each side. These nodes were therefore, as far as possible, comparable anatomically from side to side and from patient to patient. There were exceptions: sometimes no node could be found in the centre; also if the node had been used to take a direct injection of Lipiodol, with possible mechanical distortion, another was sought. The node taken was not always one filled on the lymphogram. This scheme mean that in general the worst affected nodes were not necessarily biopsied. Experience of exploring nodes in other patients with lymphoedema—for example, during bridging operations—has shown that the worst affected nodes may be difficult to find. They are often reduced to small, shrunken, fibrotic objects. Furthermore, the worst nodes often lie at a higher level than our biopsy level—that is, within the pelvis itself. Our histological findings therefore do not represent the most severe disease and give a picture which tends to under-represent the amount of fibrosis present. Selection of a node was also conditioned by the need to keep the incision small and the exploration limited in order to preserve possible adjacent collateral lymph vessels. To this end all possible lymphatics, whether dye-filled or not, were looked for and preserved and meticulous haemostasis observed. The dissection was frequently carried out with a microscope, using microvascular techniques. In no case did the biopsy ever appear to enhance oedema, but it might well do if such precautions were not observed. Routine node biopsy is not recommended as a regular diagnostic tool in lymphoedema.

In a minority of patients node material was obtained during therapeutic operations for lymphoedema. These included patients undergoing Nielubowicz lymphovenous shunts, in which a portion of a node is removed as part of the operation during its implantation into a vein, and the enteromesenteric bridge, in which nodes are opened or partly removed just below the block for the foot of the bridge to be attached.

The lymph nodes were fixed in 1% cetyl pyridium chloride in 10% formalin, sectioned, and stained with haematoxylin and eosin, Weigert's elastic stain, van Geison's stain, picro Malory violet for fibrin, Foot's stain for reticulin, and toluidine blue for mast cells. In all cases an attempt was made to cut the nodes in similar, comparable planes across the hilum.

The histological findings were compared with those in 30 normal inguinal lymph nodes obtained with the informed consent of patients undergoing surgery on varicose veins (21) or peripheral arteries (9). All the inguinal nodes from 5 fresh necropsies were also studied to ensure that there was no major histological variation in nodes taken from the inguinal region of a single patient.

LYMPH-VESSEL BIOPSIES

In 26 cases a biopsy specimen of a lymph vessel was also obtained from the dorsum of the foot. This was done at the time of lymphography, a small length of neighbouring lymph trunk being chosen, if possible, rather than the vessel actually injected with Lipiodol.

MEASUREMENT OF LYMPH-NODE FIBROSIS

The area of fibrosis was traced in each section, using a calibrated computerised light

FIG. 1 *Normal inguinal iliac lymphogram of woman aged 19 with functional pain.*

FIG. 2 *Distal hypoplasia in right lower limb with normal proximal pathways in a 32-year-old woman with history of 15 years' swelling of right lower leg. A solitary lymphatic led up through the leg and thigh to reach the inguinal node (where there is slight extravasation of contrast). Thereafter the pathways look normal.*

FIG. 3 *Proximal obstructive hypoplasia in right groin and pelvis of 36-year-old woman with swelling of right leg and thigh. Only one node is filled (there is also slight extravasation). The vessels below are distended and tortuous with filling of some fine collaterals. The lymphogram on the left is essentially normal.*

FIG. 4 *Distended lymphatics in the lower leg in another patient with proximal hypoplasia (male aged 7).*

pen and monitor. The area of fibrosis was related to the whole area of the node section. This method was highly reproducible, but each trace was performed 5 times and a mean reading taken. A mean of 9 sections were studied from each lymph node. The computer was calibrated and its accuracy assessed by focusing a millimetre graticule under the microscope and measuring the area between the lines. The computer measurement was then related to the known area on the graticule.

Results

LYMPH-NODE HISTOLOGY

The normal inguinal lymph nodes varied considerably in their appearance. Some degree of fibrosis limited to the hilar region was a normal feature (Fig. 5). Areas of hyaline fibrosis in the cortex of the lymph node were seen in a few instances. Pericortical fibrosis (thickening of the fibrous capsule) was likewise present to a certain degree in a few of the nodes from the control series. Lymphoid tissue involutes with age, and fibrolipomatosis was a feature of many lymph nodes taken from older patients.

Taking these normal variations into consideration, the most striking difference in the lymph nodes taken from the patients with lymphoedema was an *extensive fibrosis* not seen in the normal inguinal lymph nodes (Fig. 5). In the less affected nodes the fibrosis appeared as a perivascular cuff associated with intimal proliferation of patent lymphatics. Pericortical fibrosis was apparent in some of those patients who had a history of cellulitis.

From observations on some of the less affected nodes the fibrotic process appeared to emanate from the hilum and initially affect the medullary sinuses. It was associated with obliteration or appearances suggesting recanalisation of many of the adjacent vessels. There was often obliteration of the marginal sinus. In some lymph nodes there was dilatation of the lymphatics, especially in the hilum, and in others there was hypertrophy of both afferent and efferent lymphatics. Both these processes in the lymph vessels could have been caused by obstruction proximal to the lymph node that had been biopsied.

The amount of lymphoid tissue in the nodes was reduced, but what remained appeared normal. A few lymph nodes showed very active germinal centres, but this was unusual. Even in patients with large and clinically palpable inguinal nodes or a very short history of lymphoedema there was no evidence of an acute inflammatory process in the lymph nodes. The follicular architecture was not distorted, although the area of collagen fibres was increased.

In those lymph nodes with areas of normal lymphoid tissue and areas of fibrotic tissue it was not possible to determine whether the node had ever been normally formed.

No interstitial deposition of fibrin within the node was seen in the sections examined.

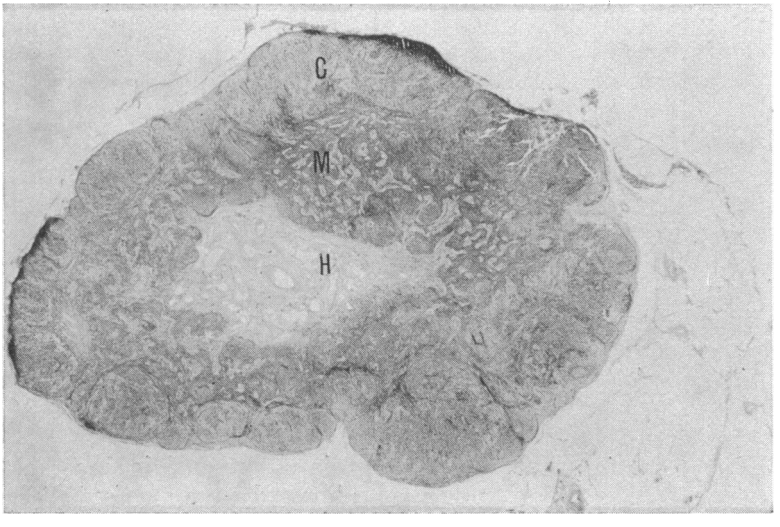

FIG. 5 *Normal inguinal lymph node from 23-year-old woman with uncomplicated primary varicose veins (9.8% fibrosis). The hilar fibrosis (H), medulla (M), and cortex (C) are marked. (Haematoxylin and eosin. ×18)*

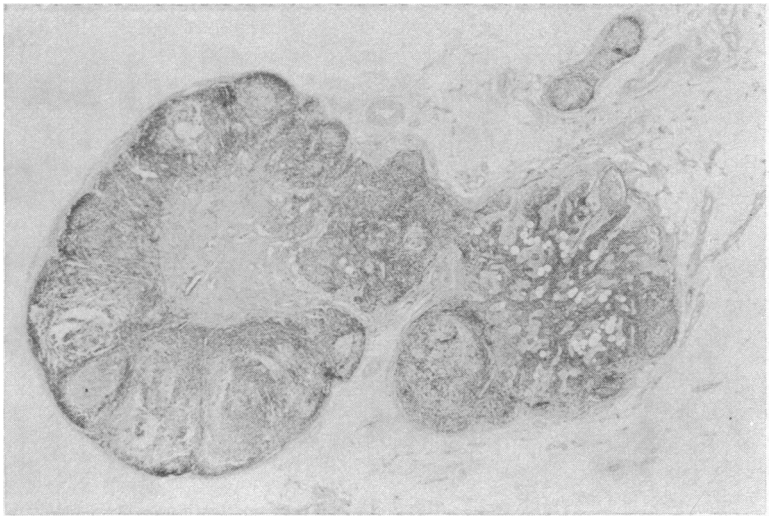

FIG. 6 *Right inguinal node from woman aged 32 with distal hypoplasia (lymphogram shown in Fig. 2). There is no abnormal fibrosis in this node (14% fibrosis). (Haematoxylin and eosin × 36)*

In the 2 patients with Milroy's disease the nodes were small and moderately fibrosed (27% and 18% fibrosis respectively). They had essentially the same changes as in lymphoedema praecox and tarda.

LYMPH-VESSEL SECTIONS

In general the changes in the foot lymphatics were similar to those in the afferent and efferent inguinal lymphatics. There was considerable intimal proliferation and hypertrophy of the muscular layer. The lumens were narrow and often showed recanalisation changes. The changes suggest a proximal obstructive process resulting in lymphatic hypertrophy, intimal proliferation, and finally obliteration.

It was interesting to note that in 1 of the 4 patients who had a foot lymphatic biopsy and proximal obstructive hypoplasia the foot lymphatic was still histologically normal although the afferent and efferent inguinal lymphatics were hypertrophic, with intimal proliferation.

The changes in the lymph vessels will be discussed further below.

MEASUREMENT OF LYMPH-NODE FIBROSIS

When the nodes were separated into groups according to the lymphangiographic findings and the measured areas of fibrosis were considered it became apparent that the patients with distal hypoplasia had a normal mean area of fibrous tissue (Fig. 6). In the patients with proximal obstructive hypoplasia, however, there was significantly more fibrosis (Fig. 7). The patients with proximal and distal hypoplasia or bilateral hypoplasia also had an abnormal amount of fibrosis in the inguinal nodes, but this was not as extensive as in patients with proximal obstructive hypoplasia. The mean area of fibrosis in the node in each group was as follows:

1) Normal (30 patients): 10%

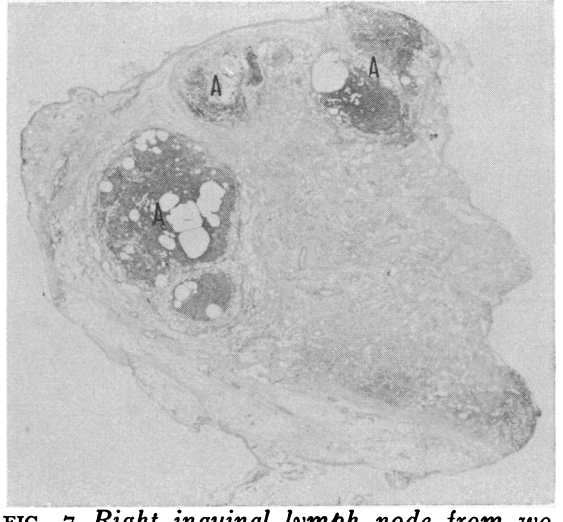

FIG. 7 *Right inguinal lymph node from woman aged 36 with obstructive hypoplasia (lymphogram shown in Fig. 3). The remaining areas of lymphoid tissue are shown (A) and the rest of node is replaced by fibrous tissue (62% fibrosis) (Haematoxylin and eosin. × 18). (N.B. The 'vacuoles' in the lymphoid areas are artefacts due to Lipiodol injection.)*

2) Distal hypoplasia (22 patients): 11%
3) Distal and proximal hypoplasia (19 patients): 34%
4) Proximal hypoplasia (19 patients): 41%
5) Hyperplasia, bilateral (11 patients): 28%
6) Unilateral megalymphatics (3 patients): 11%

By Student's *t* test there was a significant increase in fibrosis in Groups 3, 4, and 5 ($p < 0.0001$).

The fibrotic nodes were not necessarily smaller than the normal nodes. The mean area of the lymph-node sections from the patients with proximal obstructive hypoplasia was 66 mm², from those with distal hypoplasia 27 mm², and from the normal controls 25 mm². The fibrosis is therefore not due to lymph-node atrophy.

The enlargement of the nodes in proximal hypoplasia was almost certainly due to swelling of nodes lying below an area of obstruction. The inguinal nodes sometimes looked enlarged on the lymphograms in this group, particularly when the main hypoplasia lay within the pelvis. There is probably a similar explanation for the large size of the nodes in bilateral hyperplasia, but in this group the obstruction is likely to lie higher still, perhaps in the thoracic duct or region of the cisterna chyli.

In some cases more than one biopsy was performed. In 7 an inguinal node had also been taken from the clinically normal limb and there was significantly *more fibrosis in the node from the affected limb* than in that from the normal contralateral limb ($p=0.01$ by the paired *t* test). When nodes were taken from both limbs of patients with bilateral lymphoedema and compared the amount of fibrosis was very similar in the two limbs (16 pairs); the fibrosis was also similar when two nodes from the affected limb were compared (13 pairs). It was interesting to find that there was *more fibrosis in the nodes of the clinically normal contralateral limbs of patients with lymphoedema* (mean 25% fibrosis) than in nodes from patients without lymphoedema (mean 10% fibrosis) (significant to $p=0.003$ by Student's *t* test).

Clinical and lymphographic features related to lymph-node fibrosis

Since the patients with distal hypoplasia had apparently normal inguinal lymph nodes it was interesting to note the clinical differences between the groups of patients (see table).

When distal hypoplasia and proximal obstructive hypoplasia (the two extreme forms of lymphatic hypoplasia) were compared there were several striking differences. Distal hypoplasia usually produced a bilateral mild lymphoedema that never progressed proximal to the knee. Conversely proximal obstructive hypoplasia was usually a unilateral disease affecting the whole limb. Distal hypoplasia was almost exclusively a disease of females, whereas proximal obstructive hypoplasia affected males and females equally.

Clinical differences between the lymphographic types of primary lymphoedema

	Distal hypoplasia; normal proximal pathways	*Distal and proximal hypoplasia*	*Proximal obstructive hypoplasia*	*Bilateral hyperplasia*	*Megalymphatics*
No. of patients	22	19	19	11	3
Males: females	1:21	4:15	10:9	7:4	1:2
Whole-leg oedema	0	11 (58%)	17 (89%)	3 (27%)	3 (100%)
Unilateral oedema	6 (27%)	15 (79%)	18 (95%)	1 (9%)	1 (33%)
Mean duration of disease before biopsy (years)	6	5	5	11	22
Local precipitating factor	2 (9%)	4 (21%)	7 (37%)	1 (9%)	0
Family history	8	4	4	1	0

The factors associated with the onset of lymphoedema were also different in the two groups. The relationship with the age of onset of puberty was more striking in those patients with distal hypoplasia (33%) than in those with proximal obstructive hypoplasia (11%).

A clear association with congenital and hereditary factors was inferred from a family history of the disease, congenital lymphoedema, or associated congenital abnormalities. This association was apparent in 13 (59%) of the patients with distal hypoplasia: 8 of the 22 had a family history, in 3 the disease was congenital in onset, and 2 had other congenital anomalies (1 deafness and 1 skin angiomas). Only 8 (22%) of the 36 with proximal hypoplasia had such an association.

Conversely a local precipitating factor that the patient related to the onset of lymphoedema was present in only 2 (9%) of the 22 patients with distal hypoplasia (1 cutaneous infection and 1 sprained ankle), but in 7 (37%) of the 19 patients with proximal obstructive hypoplasia (2 cutaneous infections and 5 mildly traumatised lower legs). In no patient was the 'precipitating factor' a severe injury, which suggests that there was an underlying abnormality of the lymphatic system.

There were 11 patients with bilateral hyperplasia of vessels and nodes. The lymphoedema in this group may be attributed to an obstructed thoracic duct. It was opacified but was grossly abnormal in 4 patients; mediastinal nodes but no thoracic duct could be visualised in the remaining patients. The mean inguinal lymph-node fibrosis in this group was 28%.

The 3 patients with megalymphatics had no evidence of lymphatic obstruction in the limb or abdomen but had dilated, incompetent lymphatics. These were associated with cutaneous chylous vesicles in 1 patient and chylometrorrhoea in another. There was no increased fibrosis in the lymph nodes from this small group of patients. This was an interesting finding which further justified their separation into a separate group, already made on clinical and lymphographic grounds. The small number of patients available for this study is almost certainly responsible for two unrepresentative features: in larger groups the sex incidence tends to be equal and the disease almost always unilateral *(1)*.

The possible role of infection

It might be postulated that the fibrosis was secondary to attacks of cellulitis and ascending lymphangitis, but only 20 patients gave a history of previous episodes of clinical cellulitis. The mean area of fibrosis in these patients was 30% and in those who had never had a clinical attack of cellulitis it was 29%, a negligible difference. Fibrosis was therefore not related to episodes of clinical cellulitis.

Duration of the disease and degree of fibrosis

Another point to be considered is whether the fibrosis in the nodes could follow progressive obliteration of the afferent lymph vessels feeding them. If this were so one might expect the history of clinical lymphoedema to be longer in those patients with lymph-node fibrosis. The converse was true: the median duration of clinical lymphoedema before biopsy was 10 years in those patients with less than 10% fibrosis and 5.5 years in those with more than 30% fibrosis. The fibrosis was more evident in those patients with a short history of lymphoedema and it was therefore unlikely to be secondary to progressive obliteration of the lymph vessels—indeed the reverse was more likely. Further evidence that the pathological process starts within the node rather than in the vessels comes from study of the lymphograms, where dilatation can often be seen right up to the nodes themselves.

Histology of the peripheral lymph vessels

Sections of lymph vessels obtained from the foot at the time of lymphography in 26 cases showed changes similar to those seen in our earlier studies. They consisted of three main changes:

1) Subintimal thickening. This was of a hyaline nature. It produced narrowing of the lumen apparently leading to:
2) Obliteration of the whole vessel and in some cases hyaline degeneration.
3) Ectasia. Some of the vessels (almost certainly corresponding to distended vessels

seen in lymphograms) were dilated. The wall was sometimes thinned out but often showed hypertrophy of the muscle layer and reduplication of the elastic lamina.

The findings were in line with the conclusion reached in 1972 *(1)* that the histological changes were 'essentially similar in primary and secondary lymphoedema.' Our previous studies had compared patients with primary lymphoedema with others with secondary lymphoedema following block dissections (in either lower or upper limbs), radiotherapy, and excision of tumours or trauma. The histological changes in lymphatics in tropical elephantiasis (another secondary lymphoedema) were illustrated by Manson-Bahr in 1960 *(5)*. They were similar to those seen in our sections. Pfleger and her colleagues described somewhat similar histological changes in 1967 *(6)*.

The microscopic changes in the lymph vessels will be discussed in greater detail elsewhere.

Application to clinical problems

The findings confirm that patients with distal hypoplasia have the better prognosis. Only 1 of 22 patients in this group came to surgical operation. In contrast, those with proximal obstruction had a greater need for surgery, those with proximal hypoplasia alone requiring operation in 33% of cases and those with both proximal and distal hypoplasia in 37%.

The localisation of the pathological process also has a bearing on treatment. Fibrosis and severe hypoplasia if sufficiently localised to the pelvis might be more suitable for a physiological bridging operation *(7,8)*.

Our findings show that this disease is often a more widespread and diffuse process than might be thought. It was quite surprising to find an appreciable degree of unsuspected fibrosis in nodes from the contralateral, clinically normal limb. Also nodes which had looked relatively good on the lymphangiogram proved to have much fibrosis on section.

Further discussion

The important finding in the histological studies is that primary lymphoedema is associated with primary fibrosis in the lymph nodes, apparently producing obstruction. The greater the amount of fibrosis, the greater the swelling and the more rapidly it increases. No similar fibrotic process has been found in the lymph vessels, the changes in which are those of degeneration and obliteration attributable to obstruction and stagnation. A simple explanation would be to attribute all changes to fibrosis in the lymph nodes with secondary changes in the vessels.

Some explanation is, however, needed to account for the patients who showed no increased fibrosis in the nodes but had lymphographic changes in the peripheral vessels alone (distal hypoplasia). It is possible that these nodes are indeed diseased but to a degree insufficient to be detected on microscopy or lymphangiography. Abnormality might have been detected in many if the lymphadenograms had been taken into consideration. As mentioned above, for simplicity of classification only lymphangiograms were used in this study. Study of a somewhat similar group of patients in which nodes as well as vessels were examined lymphographically showed that 49 out of 55 patients had disease affecting both nodes and vessels *(4)*. We have also encountered patients with primary distal hypoplastic lymphoedema in whom the transit time of dye was slow through the nodes even though they had normal lymphadenographic appearances *(1)*. It is conceivable that minor degrees of pathological change in nodes may increase the normal resistance to flow *(9)*, producing some degree of stagnation in the peripheral lymphatics. This, if sufficiently prolonged, would produce slow obliteration of the peripheral vessels, resulting in hypoplasia or even aplasia. Such an explanation would fit with the longer history observed in such patients in this series.

The question arises of the aetiology of the fibrosis. The patients have a high incidence of familial history, congenital onset of disease, and associated non-lymphatic congenital anomalies. It must be regarded as a developmental or genetic defect showing itself in some patients at birth and in others in young or adult life. In a minority of patients only was there a precipitating factor (discussed above) such as mild trauma or inflammation. This would not produce permanent oedema in a normal subject, but in someone with an

inherent fault in the lymph nodes it might well do so. Furthermore, our biopsies of nodes from the contralateral clinically normal limbs have often shown an abnormal degree of fibrosis.

The condition of aplasia remains for consideration ('no formed lymph vessels . . .'). It has already been referred to above. It may be explained in adults as due to stagnation and degeneration of peripheral lymphatics, with final disappearance, but this is less acceptable in congenital cases. In these the vessels may never have formed at all in the embryo or they may have formed but degenerated during intrauterine life owing to fibrotic change in the nodes. This remains unsettled. Either explanation is possible.

The only study of the histology of the lymph nodes in primary lymphoedema that we have found in the literature is that of Olszewski and his colleagues *(10)*. They do not remark on the intense fibrosis that appeared so striking to us. 'Histological investigation of inguinal lymph nodes revealed normally developed structures with some degenerative changes like atrophy of lymphoid tissue and proliferation of fibrous and adipose tissue.' The last phrase might describe the fibrolipomatosis seen particularly in older patients rather than the dense areas of medullary fibrosis seen in our sections. Many of their node specimens were obtained during the operation of lymphonodovenous shunting. It is probable that they would have chosen to use as healthy as possible a node, below the blocked hypoplastic area. The specimen of tissue examined might therefore have been unrepresentative of the worst affected nodes.

Conclusions

1) Patients with primary lymphoedema may show marked fibrosis in lymph nodes.

2) The distribution and appearance of the fibrosis is quite different from that which might have resulted from inflammation. Further, the vast majority of patients have no history suggesting inflammatory attacks.

3) The amount of fibrosis varies in different clinical and lymphographic groups. It is most in proximal and in proximal plus distal lymph-vessel hypoplasia.

4) The oedema is worse and more acute in these patients with proximal hypoplasia.

5) The oedema is less widespread and often of longer duration in patients with distal hypoplasia (and relatively less fibrotic nodes).

6) Patients with bilateral hyperplasia have enlarged nodes with large areas of fibrosis and enlarged vessels. The picture probably results from obstruction at a high level such as the thoracic duct or cisterna chyli.

7) The fibrotic process is often more widespread than suspected. The nodes in clinically normal contralateral limbs are often affected.

8) The histological (and lymphographic) changes in the peripheral lymph vessels may be secondary to the fibrosis in the nodes.

9) There are many clinical features to suggest that the fibrotic process and tendency to oedema are due to a genetic or familial defect.

10) The node biopsies were performed with particular care and precaution to avoid damage to the collateral circulation. Diagnoses can normally be established by lymphography and other measures. Biopsy need not and should not be undertaken routinely.

Statistical note

Student's t test showed a significant increase in fibrosis in Groups 3, 4, and 5 ($p < 0.0001$). However, the standard deviations were high and variable (Group 1, $\pm$ 7.1%; Group 2, $\pm$ 7.1%; Group 3, $\pm$ 28.4%; Group 4, $\pm$ 23%; Group 5, $\pm$ 17%; Group 6, $\pm$ 9%). As this could invalidate the method used it was checked by taking logs of both the areas of fibrosis and the total areas of the sections and performing a covariance analysis. This compared the area of fibrosis in the groups allowing for the differing total areas of the sections, and the standard deviations on the transformed scale were comparable. This analysis showed the same differences in Groups 3, 4, and 5 but also appeared to show a difference between the control group and patients with distal hypoplasia (Group 2) ($p < 0.05$). This was partially caused by undue weight being given to 5 very low readings, 4 of which were in the control group. This last finding is of doubtful significance.

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