

## Differential Diagnosis of Lymphedema after Indirect Lymphography with Iotasul

H. Partsch<sup>1</sup>, B.I. Wenzel-Hora<sup>2</sup>, A. Urbanek<sup>1</sup>

<sup>1</sup> Vascular Service (Head: Univ.-Doz. Dr. H. Partsch) and Central X-ray Department (Head: Dr. A. Urbanek) of the Hanusch-Hospital, Vienna; Austria

<sup>2</sup> Research Laboratories of Schering Berlin (West) and Bergkamen, Federal Republic of Germany

### Summary

Indirect lymphography with Iotasul (interdigital, intradermal infusion) was performed in 32 patients with lymphedema. No side effects were observed.

Opacification of the peripheral lymph vessels reveals two distinct patterns:

1. No, few, or only very small-calibre lymph vessels ("hypoplasia"): 17 patients (primary lymphedema in 14 cases, secondary in 3).
2. Many large-calibre (dilated) lymph vessels ("hyperplasia"): 15 patients (primary lymphedema in 2 cases, secondary in 13).

An occasional finding in "hypoplasia" is drainage of the contrast material in the region of the adventitia of vessels, and a network of extremely fine lymph vessels apparently corresponding to the dermal plexus is sometimes observed.

Because it leads to the opacification of barely perceptible lymph vessels in the extreme periphery which were previously inaccessible to radiology, indirect lymphography offers a genuine gain in information and improves the differential diagnosis. When administered correctly, Iotasul invariably enhances the peripheral lymph vessels without making any great demands of the patient or investigator.

The use of direct conventional lymphography with oily contrast media for the routine clarification of lymphedema has been decreasing steadily in recent years for the following reasons:

1. side effects on the diseased lymphatic system itself and pulmonary and cerebral complications due to the oily contrast medium (3, 7);

2. the low therapeutic relevance in the majority of cases (4);
3. an adequate differential diagnosis can usually be made clinically. The simple and relatively safe method of isotope lymphography is a valuable aid (8).

Direct lymphography has nevertheless led to the differentiation of various forms of lymphedema (7), a development which has therapeutic implications in certain cases. *Kinmonth's* rough division into "hypoplasia", with few or thin lymph collectors, and "hyperplasia", with many, dilated lymph vessels, was, after all, based on the technical ability to locate and puncture a vessel of adequate calibre. Consequently, patients in whom this was not possible were almost invariably classified as "hypoplasia".

The development of a new contrast medium for indirect lymphography permits an interesting and novel view of the radiological anatomy of peripheral lymph vessels. The introduction of lymphotropic radiopaque material into interstitial tissue offers the basic possibility of observing the very start of lymph transport, a region which is not demonstrated by the conventional method. Lymphatic structures are revealed in the vicinity of the skin which have previously been inaccessible to radiology.

Findings can now be made for lymphedema which help to extend our present knowledge of the physiology and pathology of the lymphatic system.

Table 1

		Lower extremity		Upper extremity	
		female	male	female	male
Primary lymphedema 17	congenital-hereditary (Nonne-Milroy)	2 (bilateral)			
	congenital-non-hereditary	3 (1 Klippel-Trenaunay)		1	
	Lymphedema precox	5			
	Lymphedema tardum	7			
Secondary lymphedema 15	after surgery for malignant growth and postoperative irradiation	1	4	4	
	post-inflammatory (erysipelas)	2	2		
	artificial (tourniquet)			2	

### Examination technique

The studies were conducted with Iotasul\*, a non-ionic, water-soluble, dimeric contrast medium. Its excellent tolerance has been demonstrated in numerous animal and clinical studies. The lymph vessels are invariably visualized when the correct administration technique is used (1, 5, 6, 9, 10, 11, 12, 13).

In contrast to our studies in animals, injection of the contrast medium in the periphery of the extremities of man — the subject of this paper — has so far failed to achieve satisfactory visualization of the lymph nodes.

In all our patients, Iotasul was infused subepidermally into the proximal, dorsal areas of the interdigital folds of the hands or feet by means of a motorized pump (Perfusor®; Braun, Melsungen) converted for 4 syringes. The amount of contrast medium administered was 10 ml per extremity, i.e. 2 x 5 ml, which was contained in disposable syringes with butterfly cannulae. The rate of infusion was 0.1 to 0.15 ml/min. In some cases, 15 and 20 ml contrast medium were infused via 3 or 4 injection sites per extremity (SIL = simultaneous indirect lymphography).

In others, the injection was also given behind and below the external malleolus (demonstration of the posterior prefascial tract) and on the medial side of the proximal upper and lower leg. Verruciform lymphangioma cysts were found to be excellent injection sites for good lymphangiography.

Strictly subepidermal positioning of the injection cannula is of vital importance during the intracutaneous injection, and the following procedure has proved successful:

Insert the cannula and lift a small fold of skin with it; advance the cannula, pushing upwards towards the surface and stopping just before the tip penetrates through the epidermis. During the injection, the contrast medium should glisten through like porcelain in the vicinity of the cannula tip.

The patients experience moderate, burning pain at the start of the infusion, but this regresses after a few minutes. No objective side effects have been observed to date. The wheals which develop are completely absorbed again within a few hours.

The findings were documented by fluoroscopy with high-resolution films and screen cassettes.

\* Schering AG, Berlin

### Patients

32 patients with lymphedema of the extremities of varying origin were examined (26 women and 6 men aged between 17 and 70 years).

In all instances of lymphedema, a disturbance of prefascial lymph transport was demonstrated by isotope lymphography ( $^{99m}\text{Tc-S-colloid}$ ).

Direct caudal lymphography was performed additionally for oncological reasons in one male patient presenting with hypernephroma metastases in the inguinal lymph nodes.

The study also included 2 female patients with *Nonne-Milroy's* disease in whom attempts to expose a lymph vessel on the dorsum of the foot for direct lymphography had been unsuccessful; histological examination failed to reveal any definite lymph vessels.\*

### Results

Indirect lymphography with Iotasul using high-resolution films reveals two distinct patterns of peripheral lymph vessels:

1. No, few or only very small-calibre lymph vessels ("hypoplasia"). Rarely, broad bands of contrast medium are found which apparently correspond to clearance in the adventitia of blood vessels (Fig. 1).
2. Many, large-calibre (dilated) lymph vessels ("hyperplasia") (Fig. 2 and 3).

Table 2 shows the frequency of these two main patterns in our lymphedema patients.

To make the findings comparable with *Kinmonth's* classification, only the number and the calibre of larger peripheral lymph vessels which would also be accessible to direct lymphography can be considered for the rough division into "hypoplasia" and "hyperplasia".

However, very much finer lymph vessels can be visualized with indirect lymphography — a very dense network of extremely fine vessels which cannot be demonstrated by the direct administration technique is a frequent finding in patients with numerical "hypoplasia"



**Fig. 1** 20-year old female patient with congenital, hereditary lymphedema (*Nonne-Milroy's* disease). Following indirect lymphography, drainage of the contrast medium under light massage in the region of the adventitia of blood vessels ( $\uparrow$ ). No demonstration of lymph vessels ("hypoplasia", aplasia?)

of the larger lymph vessels (Fig. 4). They probably correspond to the dermal plexus which acts as a collateral circulation.

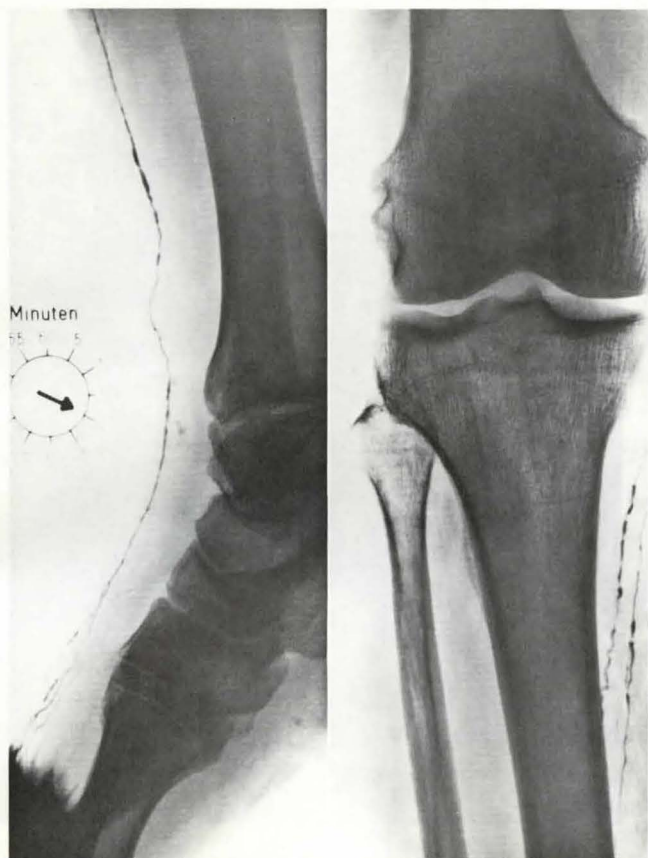
Structurally similar networks — albeit with a plexus of greatly dilated, varicose lymph vessels — classified as "hyperplasia" are found mainly in secondary lymphedema (Fig. 5). or in primary forms which we regard as "proximal hypoplasia with distal distension" (7).

### Discussion

The advantages of indirect lymphography are obvious:

the method is simple, places little stress on the

\*These 2 cases with the pertinent findings were kindly referred by Prof. Dr. E. Mannheimer, Vienna



**Fig. 2** Dilated and congested lymph vessels in a male patient with inguinal lymph node metastases from a hypernephroma ("hyperplasia")

**Table 2**

		"Hypoplasia"	"Hyperplasia"
Primary lymphedema	14	2 congenital-hereditary	3
		2 congenital-non-hereditary	
		4 lymphedema praecox	
		6 lymphedema tardum	
Secondary lymphedema	2	after surgery for malignant growth and postoperative irradiation	7 after surgery for malignant growth and postoperative irradiation
			4 after recurrence and erysipelas
			2 after artefact
			13



**Fig. 3a**

**Fig. 3a** Dilatation and irregular course of lymph vessels in the hand and distal forearm of a female patient after mastectomy and postoperative irradiation



**Fig. 3b**

**Fig. 3b** Dermal black-flow in the region of the ulnar tract ("hyperplasia")

**Fig. 4** 23-year old female patient with lymphedema precox. Normal lymph channels on the healthy side (right), dense network of extremely fine vessels corresponding to a dermal plexus on the edematous side (left). Since these lymph vessels must be seen as collaterals and there are no normal collectors which can be followed into the lower leg, classification as "hypoplasia"





**Fig. 5** 38-year old male patient with lymphedema after 46 episodes of erysipelas. Injection into a lymph cyst at the base of the 2nd and 3rd toe, after which the lymph vessels opacified "directly" without the formation of wheals. Dense network of dilated lymph vessels with dermal back-flow ("hyperplasia")

patient, and produces information about the peripheral lymph vessels at all levels of the extremity.

Investigation of the lymph drainage of the skin requires strictly subepidermal injection. The lymph vessels do not usually enhance following subcutaneous or intramuscular injection, and visualization of the lymph nodes is inadequate on purely peripheral, intracutaneous administration.

The main advantage over direct lymphography as regards the yield lies, in our opinion,

in the demonstrability of small-calibre, extremely fine peripheral lymph vessels which have previously always escaped radiological visualization. Structures of this size can only be demonstrated by direct lymphography if they are incompetent or exhibit reflux (dermal back-flow).

With indirect lymphography, on the other hand, we can also demonstrate normal vessels which — as in a healthy hand (Fig. 6) — are so fine that they could not be punctured for direct investigation. We are therefore dealing with a dimension which lies between fluorescence microlymphangiography (2) and direct contrast lymphography.

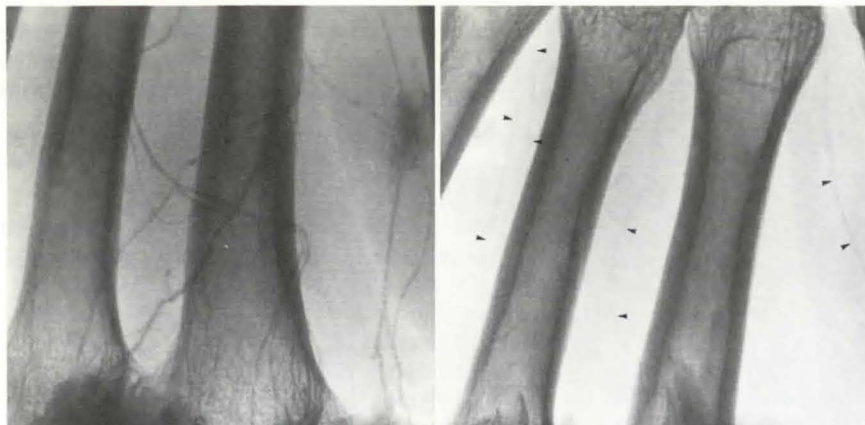
In agreement with *Kinmonth's* results, "hypoplasia" of the larger peripheral lymph vessels predominates in primary lymphedema. In many of these cases, however, the use of high-resolution films reveals opacification of extremely fine networks of lymph vessels (Fig. 4) which apparently correspond to the cutaneous plexus. Numerical "hypoplasia" of the subcutaneous lymph collectors is accompanied here by numerical "hyperplasia" of the cutaneous plexus (precollectors). Our findings in Milroy's disease may be caused by aplasia of lymph vessels.

We found peripheral "hyperplasia" with dense networks of dilated dermal plexuses in only three cases of primary lymphedema (Fig. 5), and these may well be due to "proximal hypoplasia with distal distension". In these cases the intralymphatic pressure is probably greatly increased, and had led to the formation of verruciform lymphangioma cysts in the toes.

Hyperplastic variants predominate in the secondary forms of lymphedema. A possible explanation for subsequent "hypoplasia" is secondary fusion or obliteration of congested lymph vessels in the course of the disease.

Our findings with indirect lymphography have two main implications for practice:

1. Patients with distal "hypoplasia", who are not eligible for a lymphovenous shunt operation, can be reliably identified with this simple method.
2. Visualization of lymph vessels in the extreme periphery which are just visible to the naked eye is vital for clarification of



**Fig. 6** 20-year old woman with artificial lymphedema consequent to the application of a tourniquet to the upper arm.

Right the healthy hand with extremely fine, barely perceptible lymph vessels (↑), left the diseased side with congested vessels. Demonstration in the region of the metacarpal bones

the pathophysiology of lymphedema, and could well lead to modification of the present classification of the disease.

Magnification techniques should increase the yield even further.

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*Univ.-Doz. Dr. H. Partsch, Vascular Service, Hanusch-Hospital, A-1140 Wien, Austria*