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USE OF THE C-SCAN IN EVALUATION OF PERIPHERAL LYMPHEDEMA

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ABSTRACT

The C-(cutaneous)-scan constitutes a simple way to evaluate the status of the lymphatic system of swollen and apparently normal extremities. We have termed the procedure C-scan because this expression emphasizes the injection of the radiotracer into the cutis. Only one scintiscan, which takes approximately 15 minutes, is performed 3 hours after injection, in contrast to other investigative procedures including standard lymphangioscintigraphy, which utilize multiple scannings that unnecessarily prolong the duration of the study. The C-scan method is semi-quantitative and distinguishes pathologic conditions of the lymphatic system by means of whole body scintigraphy and by measuring the radioactivity in specific regions of interest rather than by examining solely differences in delay of transport. Both a qualitative image and a quantitative assessment are thereby produced. The C-scan is performed using a general purpose gamma camera in line to a multiprocessor computer system. Scintiscanning is performed 3 hours after an intracutaneous injection of 20 MBq of Tc99m nanocolloid (Solco) distally into the dorsum of the extremity. The image obtained is divided into regions of interest and the radioactivity in these regions is calculated as the percentage of the total radioactivity counted. The C-scan is easy to perform and can be repeated if necessary every 2 days. The effects of various treatments of lymphedema, either non-operative or operative, can be assessed short-term, and examples are provided. In conjunction with limb volume measurements, the C-scan gives an accurate impression of changes in the lymphedematous extremity before, during, and after treatment. Applications of this imaging technique are shown after combined "decongestive" physiotherapy, lymph-venous anastomosis, ablative (debulking) surgery, liposuction, and thermotherapy.

Evaluation of lymphedema and its treatment has been hampered by a simple and reliable technique to image the peripheral lymphatic system and quantify lymphatic transport. Although conventional lymphography using oil contrast has been in vogue for a long time, complications of oil embolism, lymphatic endothelial damage, and the cumbersome nature of the procedure have limited its usefulness. In 1967 (1), we first examined the value of radiotracer lymphography to visualize the peripheral lymphatic system. More recently, isotope lymphography has been advocated as the preferred screening test (2-6) but as practiced in many centers with multiple images over several hours is unnecessarily time-consuming.

We now describe a variation of lymphangioscintigraphy which we have termed cutaneous or C-scan, which dramatically simplifies both lymphatic imaging while allowing semi-quantification of lymph transport. The C-scan when combined with limb volume measurements can also elucidate the effect of treatment of a lymphedematous extremity.

Technique

In the dorsum of one hand or foot, 20 MBq of Tc99m Solco nanocoll (Sorin Biomedica S p.A., Vercelli, Italy) in a volume of 0.1 ml is injected intracutaneously with a long track (to avoid back leakage) using a tuberculin syringe and a 26 gauge needle. Immediately after injection, liver radioactivity is ascertained. If any activity above background is detected, the study is aborted and rescheduled for another day. If no liver radioactivity is detected, the patient is instructed to walk around and return in 3 hours for the final scintiscan. Then after voluntary voiding, a whole body scintiscan is carried out using a rectangular gamma camera (General Electric Starcam), on-line connected to a computer system. The patient is passed beneath the camera in the supine position starting at the feet with a movement speed of 0.143 m/min (128x512 matrix). The gamma camera is positioned as close to the patient as possible.

The collected data are stored by a multiprocessor computer system, and a display of the image is produced, which constitutes the qualitative or image part of the study. Regions of interest are selected to obtain quantitative information. Radioactivity at the injection site is measured in an area of 5x5 cm corresponding with 12x12 pixels.

Regions of Interest

Although the C-scan method is semiquantitative, for purposes of accuracy the regions of interest should be carefully defined. Tracer clearance represents the disappearance of the radiopharmaceutical from the injection site, which constitutes an area of skin surface of 5x5 cm. The latter surface should be measured in a small and well-defined area and not in the whole foot region, which may contain dermal backflow radioactivity. The radioactivity of the whole foot or hand region minus the radioactivity at the injection site represents the activity of the foot/hand itself. The lower leg region extends to the knee joint. The popliteal nodes, if visible, are considered to belong to the upper leg. The distal transit activity is the summation of the activities of the lower leg and foot.

The upper leg region is cranially confined by Cloquet's node, which is considered part of the inguinal region. The inguinal region is caudally limited by the lower border of Cloquet's node and the cranial limit is a horizontal line situated 11 cm above the symphysis pubis, which corresponds with an extension of 25 pixels. Of note, the medial limit excludes radioactivity in the urinary bladder. The borders of the region of the liver are considered to coincide with its visible image, but if there is renal radioactivity, the kidney region has to be excluded.

Analogous to the legs, similar principles apply for the arm. The axillary region is laterally confined by an imaginary line running sagittally through the axillary fold. Radioactivity in the whole hand/foot or the lower arm/leg, the upper arm/leg, and the axillary or groin region is measured. Finally, the radioactivity of the liver is determined. With bilateral limb investigations, hepatic radioactivity originates from both sides and accordingly, only one side is investigated at a time. The total number of counts of the whole body scan, corrected for background is taken as 100% and the radioactivity in the regions of interest is calculated as a percentage of this value after correction for background radioactivity. A simple computer program calculates these data. The rapid decay of the isotope (half-life of 6 hours) permits, if desired, the study to be repeated in 2 or 3 days, which together with measurements of volume change in the arm or leg provides assessment of treatment efficacy in lymphedematous extremities.

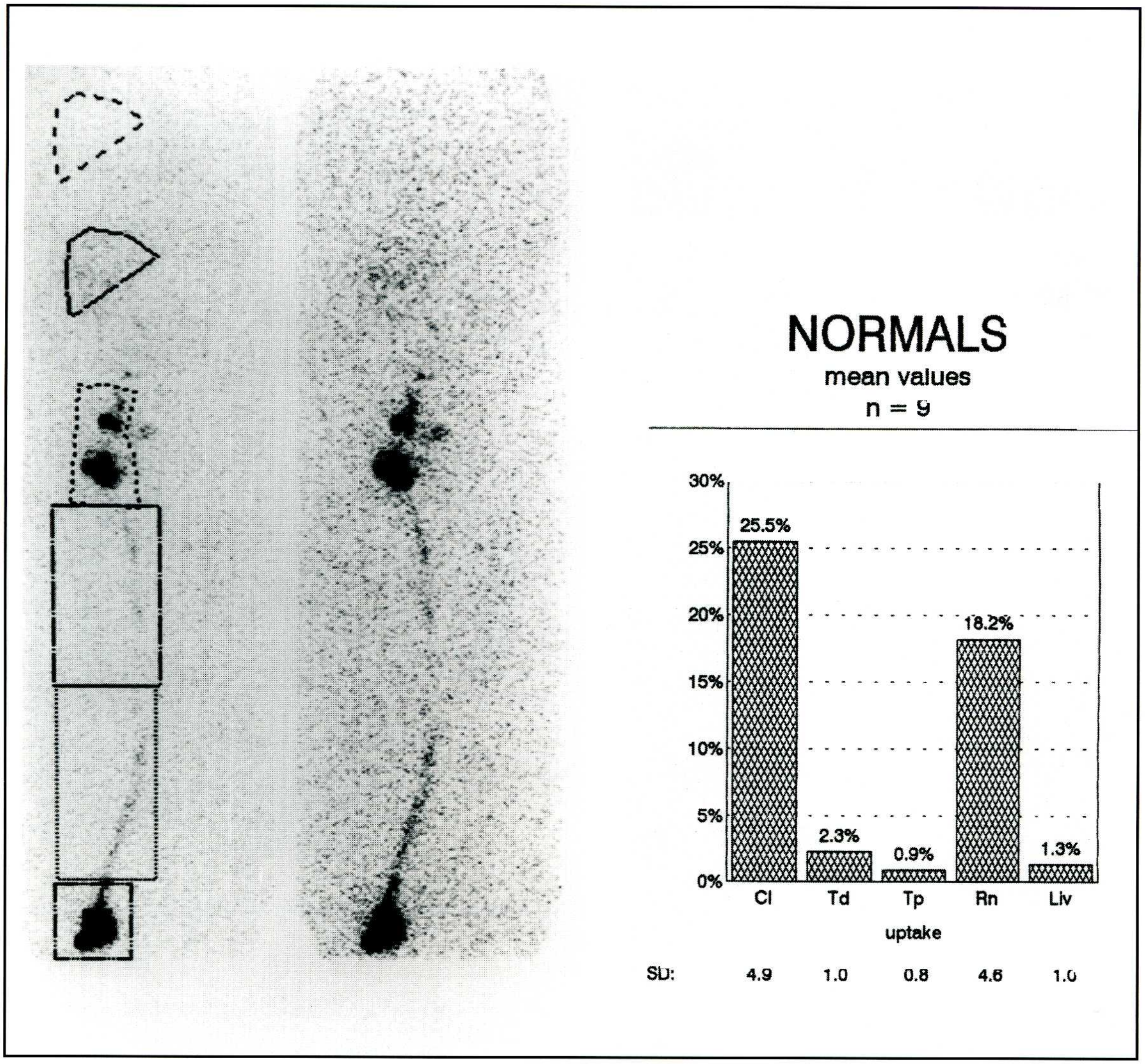

Fig. 1. Normal C-scan. LEFT) Normal image and regions of interest. RIGHT) Normal histogram: values represent percentage of total body radioactivity. CL=clearance, Td=distal transit activity, Tp=proximal transit activity, Rn=activity of the regional nodes, LIV=activity of the liver.

Many workers have recommended isotope lymphography for purposes of evaluation of lymphedema; few, however, have recommended it for evaluation of treatment (7). Beyond clinical criteria, most investigators favor an objective assessment of the effects of non-operative or operative treatment with quantitative data. The C-scan provides such a tool.

In normal legs, the radionuclide is transported by lymph collectors to the regional nodes. Activity measured in the lower and upper leg amounts to 1-2% of the total body activity and represents the tracer in transit within the lymphatics. In lymphedema, due to blockage of the proximal lymphatic system, the activity may increase to 20-30% due to dermal backflow. The tracer that

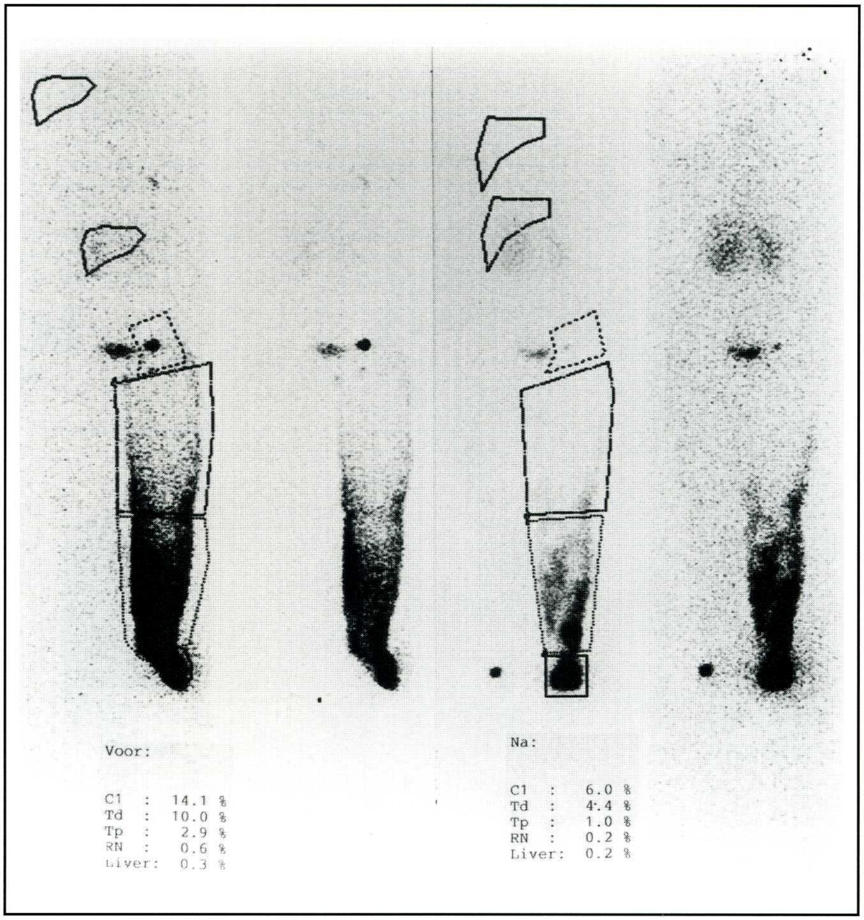

Fig. 2. Patient with tropical elephantiasis before (left) and after (right) decongestive therapy. The leg lost greater than 7300 ml of volume. After treatment, the histogram is markedly depressed. (See Fig. 1 for definition of abbreviations.).

disappears from the injection site appears in the inguinoiliac region as uptake by the lymph nodes. The mean value of activity in these regional nodes is normally 18%, which conforms to that found by others (2). Minimal uptake we found has been 9%. Liver activity depends upon several factors but usually approximates 1% of the total body activity. These normal values are derived from normal (contralateral) legs of patients with unilateral secondary lymphedema mostly due to trauma and from healthy volunteers including one of the authors. The setting of the regions of interest together with a normal histogram is shown in *Fig. 1*.

Clinical Experience

Non-operative treatment of lymphedema

Non-operative procedures for peripheral lymphedema include bedrest, intermittent external compression, manual lymph drainage, and combined physiotherapy. The clinical result is maintained by wearing of an elastic stocking. Initially in such treatment, a decrease of volume occurs with an increase in tracer clearance due to reduction of the tissue bulk and the intracapillary lymphatic pressure. Like a squeezed sponge, the lymph capillaries are able to absorb more of the injected radionuclide, which is reflected by increased transit activity and clearance. Continued treatment causes further reduction of volume and the C-scan shows diminished

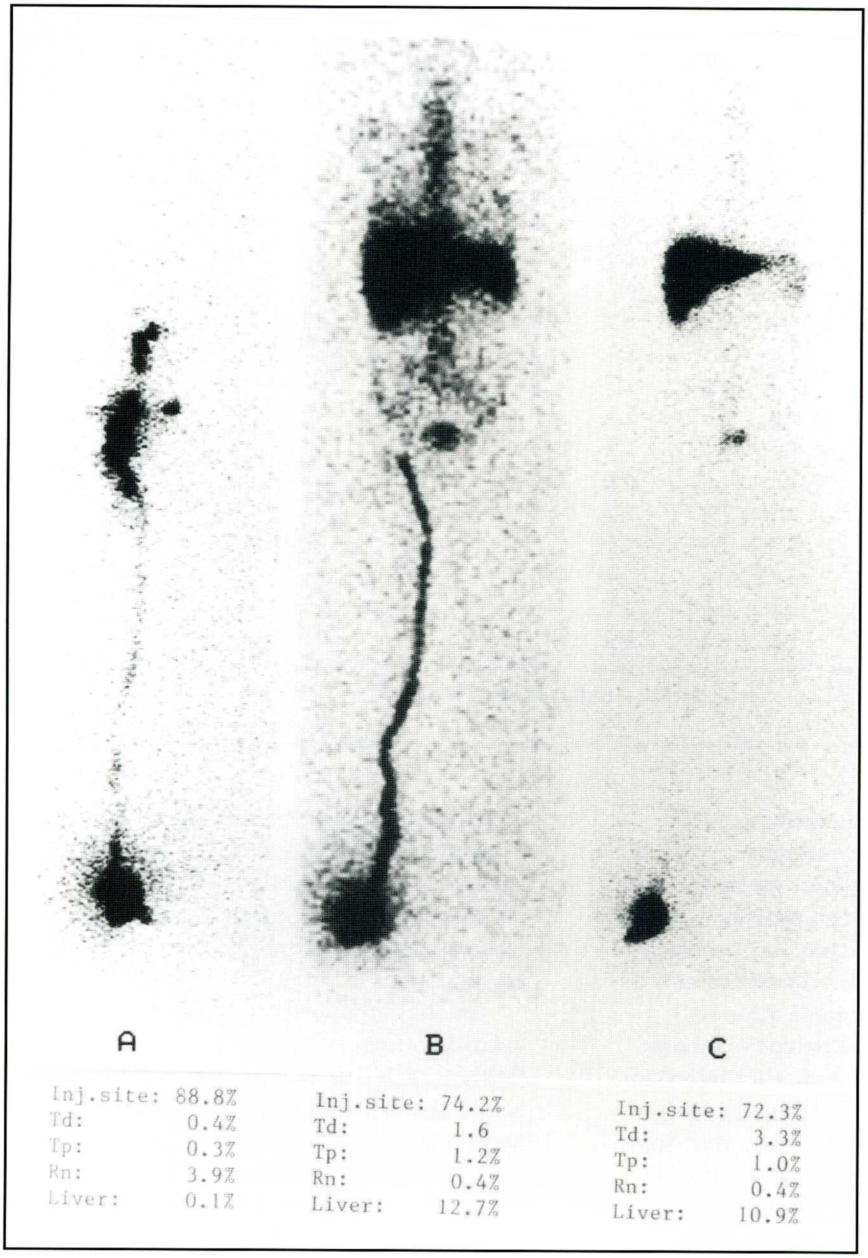

Fig. 3. Serial C-scans in a patient with primary lymphedema of the right leg, penis and scrotum. In the right groin, a thick walled lymphatic was found at operation (2 mm in diameter) and a lymphatico-venous anastomosis was constructed. A. C-scan before operation. B. Immediately after operation. C. Two years later. Note substantially improved clearance with higher liver activity after the L-V shunts suggesting patency. (See Fig. 1 for definition of abbreviations.)

transit activity and a decrease in regional nodal and hepatic uptake. The histogram is thus "depressed." This depression may derive from obliteration of lymph capillaries by external pressure. With continued treatment, the histogram becomes still further depressed signifying considerable reduction in lymph formation *(Fig. 2)*.

Lymphatic-venous shunts

The ideal treatment of lymphedema is restoration of lymphatic drainage. Many operations have been recommended in this regard including more recently lymphatic-venous (L-V) shunts (8-12). Nonetheless, doubts persist about the efficacy of these

TABLE 1
Imaging and Histogram Data (% Radioactive Uptake) in Patients After Failed L-V Shunts

Patient	Edema Duration (yrs)	T_d (%)	T_p (%)	Regional nodes (%)	Liver (%)	Popliteal node (Y/N)	Lymph vessels (Y/N)	Backflow (Y/N)
1	12	3.3	1.6	1.3	0.9	N	N	Y
2	5	1.0	1.4	1.6	0.2	Y	N	Y
3	10	4.3	0.8	0.7	0.3	Y	?	N
4	9	0.8	0.5	0.1	0.1	N	?	N
5	0.5	2.8	0.8	0.2	0.5	N	N	Y
6	1	2.0	1.2	1.3	0.6	N	N	N
7	15	6.0	0.9	2.7	0.8	Y	N	Y
8	13	1.4	0.5	1.2	0.3	Y	N	Y
9	1	3.5	1.0	0.3	0.3	N	N	Y
10	21	0.9	1.4	3.0	0.3	Y	?	N
11	40	0.7	0.5	0.6	0.3	N	N	N
12	20	1.7	0.5	0.4	0.2	N	N	N
	$\bar{x}$ 12	2.4	0.9	1.1	0.4			
	sd 11	1.6	0.4	0.9	0.2			

T_d =distal transit activity; T_p =proximal transit activity; Y=yes; N=no

operations, which are often combined with other non-operative treatments such as elastic support garment. Some authors maintain that no beneficial effect of such an operation can be expected when lymphedema has persisted longer than several months (12). Recurrent erysipelas is another contraindication to operative reconstruction. O'Brien (13) claims that diffuse coloring of the foot after injection of patent blue violet is a poor prognostic sign for embarking on a L-V shunt operation. So, too, is marked swelling. The good results of the operations seem to be of short duration; yet, others claim that edema improves over the course of time (8,11).

The variety of opinions concerning indications and results of operative treatment emphasizes the need for objective evaluation. Until now, no reliable method has existed to verify patency of a L-V anastomosis, and by and large a decrease in limb volume has been considered sufficient substantiation. However, nearly every type of non-operative treatment including bedrest with limb elevation, which invariably accompanies operative treatment, also favors limb reduction. The C-scan provides evidence of anastomotic function when performed before and after L-V anastomosis.

In our clinic, several lymphatic shunt operations have been performed in standard fashion: each patient was admitted 4 days before operation and "decongestive" treatment (bedrest, elevation of the limb, and intermittent external compression) was instituted. Twelve hours preoperatively, the volume of the extremity was measured and a C-scan performed. These studies were repeated 7 days after L-V shunt operation. The patient was instructed to move the extremity frequently in the post-operative period to facilitate lymph flow through the anastomosis.

The following changes in the histogram were considered confirmatory of a patent anastomosis:

1. Decreased transit activity distal to the anastomotic site.

2. Decreased activity of the regional nodes (if present before the operation) due to transection of afferent lymph vessels.

3. Increased liver activity due to bypassing the regional nodes. The radionuclide reaches the bloodstream earlier and is trapped by the liver.

4. The limb volume is already reduced by preoperative bedrest and intermittent compression and should be maintained and certainly not increased.

Fig. 3 illustrates these phenomena.

In a group of 12 patients with leg lymphedema, findings during the operation were mainly fibrotic lymphatics with small lumina (equal to or less than 0.2 mm). Other patients had wide and tortuous lymphatics which contained stagnant lymph. There was no flow in these lymphatics, and the lymph showed no blue coloring after injection of patent blue violet distal to the shunt site. It was not possible to promote functioning L-V anastomosis in these patients, and none had lymph flow into the venous lumen. Reduction of limb volume obtained by non-operative treatment during the 4 preoperative days was more or less maintained. This group was taken to match preoperative C-scans with perioperative findings. The results are summarized in *Table 1.*

These data suggest that a shunt procedure for lymphedema is irrational when after 4 days of decongestive therapy the C-scan shows a groin peak <3% of the total body activity without definite truncal streamers. Gloviczki et al (6) claims that in the absence of streamers, lymphatic shunt operations are doomed to failure. In one patient he nonetheless found suitable lymphatics at operation which were not depicted on the preoperative scintiscan. Presumably, obstructed proximal lymphatics do not allow the nanocoll to enter the lymph vessel. Decongestive treatment may promote this effect by reduction in tissue pressure and intralymphatic pressure. If, however, after 4 days of "decongestion" no lymphatics are depicted, success cannot be expected from a lymphatic shunt operation.

Of these 12 patients, 9 had secondary lymphedema and 3 primary. Each of the primary lymphedema patients and 5 of the secondary lymphedemas had sustained one or more episodes of erysipelas. Mean reduction of limb volume 7 days after the shunt was 308 cc, most likely due to non-operative therapy (i.e., bedrest and limb elevation). If an L-V anastomosis is functioning, the C-scan image changes. Proximal to the shunt site, structures are altered or disappear because they have been bypassed as hepatic activity increases. In this way, the C-scan is able to delineate the fate of L-V shunt on both a short-term and long-term basis.

Debulking

In many patients, non-operative treatment is ineffective primarily due to improper application, and lymphedema deteriorates into an elephantine state. These patients are typically treated by decortication (debulking) either limited (staged excision or Sistrunk procedure) or radical excision (Charles procedure). The operation removes the excess lymphedematous subcutaneous tissue and skin but fails to improve lymph transport. C-scan changes before and after such an operation are shown in *Fig. 4.* After a radical decortication, lymphatic transport is markedly curtailed, the C-scan shows little or no tracer clearance, and the histogram is markedly depressed. Of interest, a similar pattern is seen after prolonged non-operative treatment *(Fig. 5).*

Liposuction

In lymphedema the subcutaneous compartment is characteristically increased not only with edema fluid but also with fatty tissue. Accordingly, liposuction has been advocated as treatment (8). In our experience in treating lipodystrophy by liposuction,

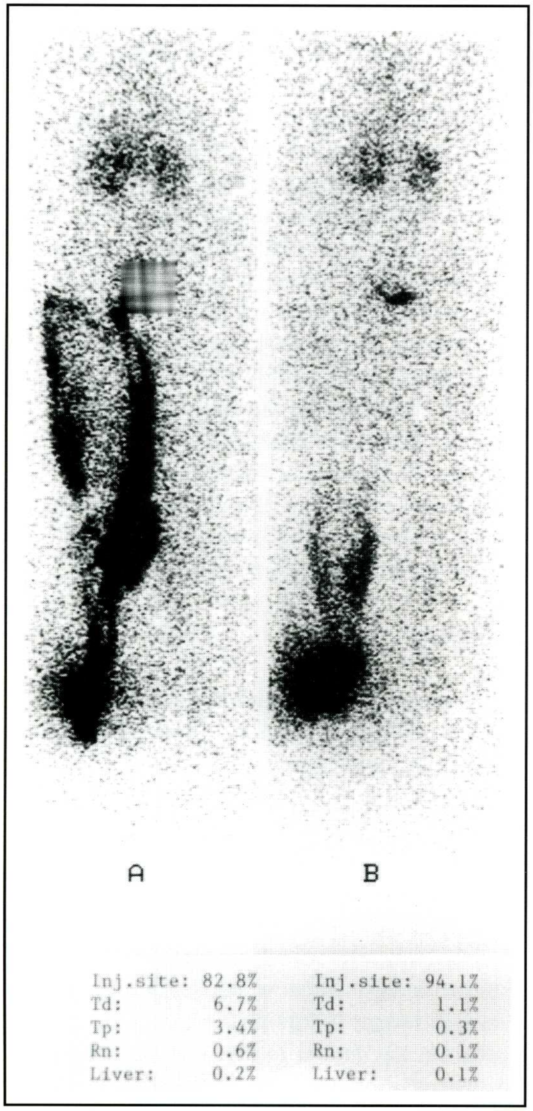

Fig. 4. A. C-scan of an elephantine leg before a partial debulking of the upper and lower leg. 3000 g of fibrotic lymphedematous tissue was removed. B. C-scan 10 days post-operatively showing reduced tracer transport and depression of the histogram. (See Fig. 1 for definition of abbreviations.)

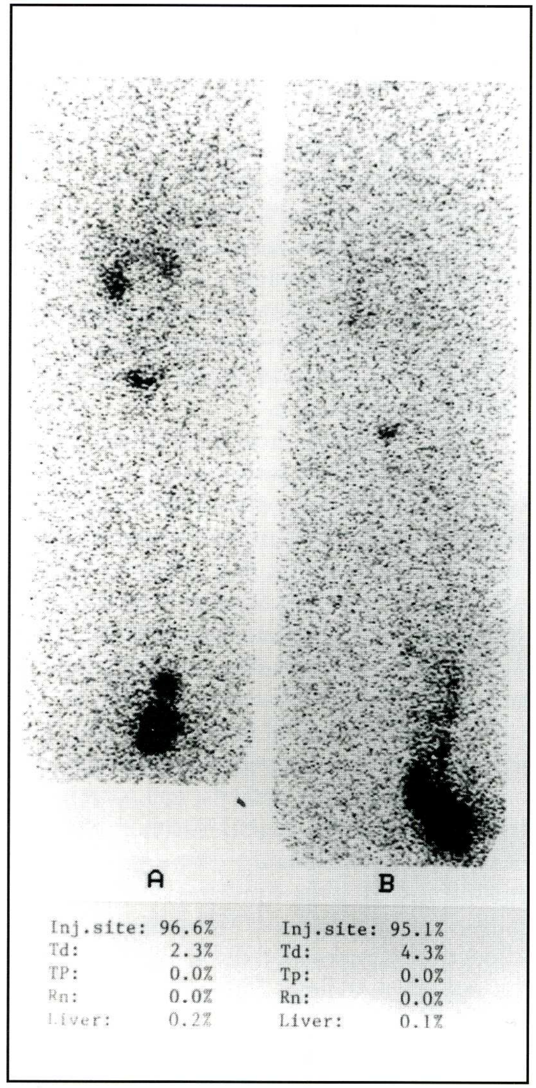

Fig. 5. A. C-scan of a patient with primary lymphedema treated non-operatively for more than 25 years. B. C-scan of a patient after radical debulking for lymphedema. Note both images (A and B) show a markedly depressed histogram. Operative and non-operative treatment may display similar C-scintigrams.

patients often develop slight ankle edema. Contrast lymphangiography has shown little or no damage to the lymph collectors (14). Nonetheless, the persistence of postoperative edema in these patients prompted us to investigate these legs using the C-scan. Each leg that underwent liposuction of the lower leg and/or knee area showed damage to the lymphatic system despite unremarkable contrast lymphography. Specifically in the C-scan, transit activity was increased in each leg studied *(Fig. 6)*.

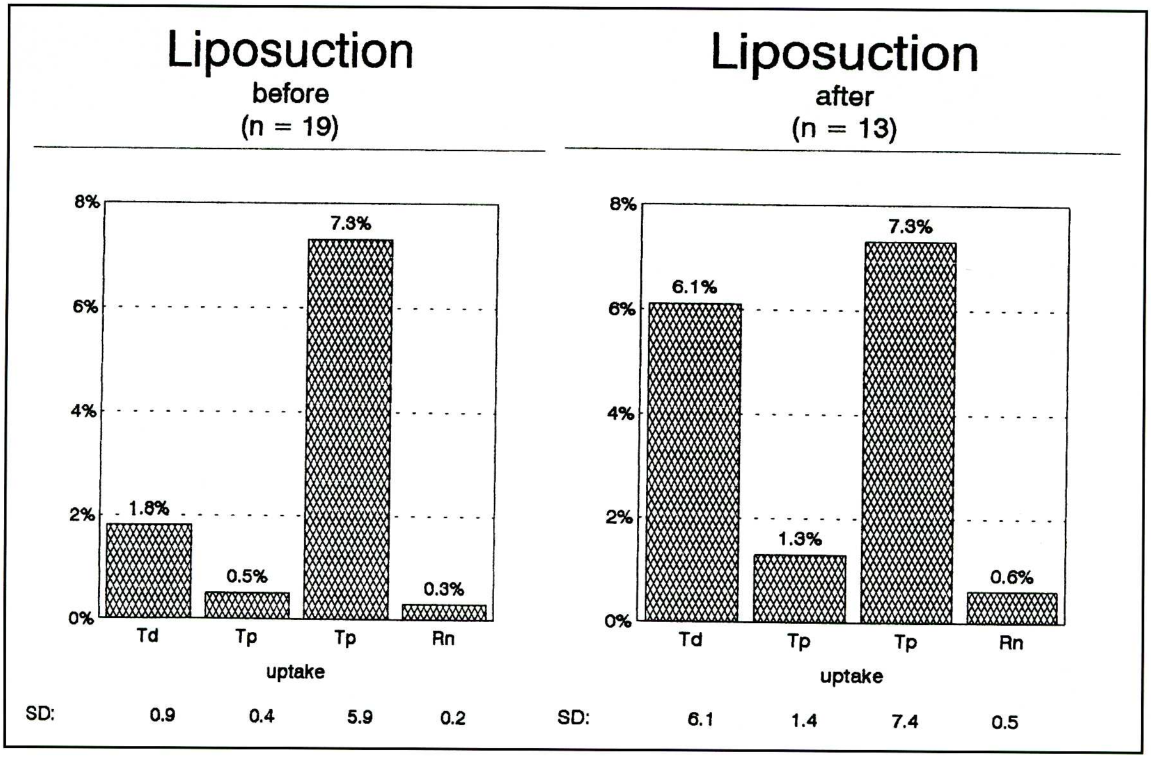

Fig. 6. LEFT) Histogram of legs of lipodystrophy patients before liposuction of the knees and/or lower legs was undertaken. RIGHT) Post-liposuction legs showing a somewhat different histogram characterized by greater distal transit activity (T_d). Tracer transport overall was not altered. (See Fig. 1 for definition of abbreviations.)

Use of liposuction in lymphedema is limited because of fibrotic changes in the subcutis. Damage to the fine structures of the lymphatic system and lymph capillaries can further aggravate an already impaired lymphatic circulation and worsen lymph stasis and fibrosis. One should recognize this possibility, and treatment of lymphedema patients by liposuction should be carefully monitored using the C-scan to document the effects.

Thermotherapy

Heat has been used to treat lymphedema (15,16). Confirmations of salutary effects and mechanisms of actions have been suggested (17,18). In our clinic, thermotherapy consists of heat application (paraffin wax at 42°C to the lower leg or arm for 45 minutes) followed by limb bandage-wrapping. This treatment is administered daily for 3 weeks. A decrease of limb volume is evident in about half the legs after one or two courses of treatment. Volume measurements and C-scan are made before and after treatment.

In a series of 40 lymphedematous extremities *(Table 2)*, an enhanced histogram was seen in 11 patients. Radioactivity of the regional nodes and liver was increased but sometimes only slightly. Despite increased tracer clearance, there may not be increased liver activity as tracer pools in the lower arm *(Fig. 7)*. Chang et al (15) found a higher uptake of 198 Au colloid in the regional nodes in 6 of 17 extremities after thermotherapy. In our patients enhancement of the histogram (i.e., tracer transport occurred and the lymphatic system was not completely obstructed) was seen in 11 patients. Yet in 4 patients, no decrease in

TABLE 2
Correlation Between the C-Scan Histogram and the Changes of Limb Volume in 40 Extremities Treated by Thermotherapy

Volume	Decreased	No Change	Increased
Enhanced Histogram	7	1	3
Depressed Histogram	7	1	2
T_d increased	5	2	6
T_p decreased	2	1	2
Unchanged Histogram	0	1	0
Total	21	6	13

T_d = distal transit activity; T_p = proximal transit activity

limb volume was demonstrated. In the remaining 29 extremities, a decrease of limb volume was found. This disparity between lymph transport and limb volume reduction requires an explanation. Hyperthermia promotes hyperemia and accordingly favors an increase in net capillary filtration and lymph load. Bandaging, however, counter-balances blood capillary filtration by augmenting tissue hydrostatic pressure. The putative beneficial effects of thermotherapy have been suggested by several investigators. Chang et al (15) found improved lymph flow and increased tracer clearance. But as already noted, increased clearance itself is insufficient documentation of improved function of the lymphatic system because the tracer may leave the injection site but pool in the lower leg. Lack of transport to the blood vascular system by absence of increased activity in the liver conforms to this viewpoint *(Fig. 7)*. Liu and Olszewski (18) suggest the breakdown of tissue protein molecules after thermotherapy. If this phenomenon occurs, however, protein (nanocoll) fragments or free technetium should appear in the bloodstream and be picked up by the liver and/or thyroid; this did not occur. Liu and Olszewski (18) also describe after thermotherapy a reduction in inflammatory infiltrate that is typically seen in chronic lymphedematous tissue and suggest that this occurrence decreases the protein content of the tissue and thereby diminishes edema. Perhaps this is a major factor in reduction of limb volume after thermotherapy.

Another potential factor which may contribute to the presumed beneficial effect of thermotherapy is altered (diminished) viscosity of the intercellular ground substance thereby facilitating migration of water, electrolytes, and particulates. “Softening” of the ground substance theoretically improves the compressive effect of bandage-wrapping thereby favoring reduction of limb volume by mobilizing water and electrolytes. In a small number of extremities, protein molecular transport was enhanced through the lymphatic system as demonstrated by an increase of liver radioactivity. In most, however, no transport of nanocoll to the blood vascular system is seen. Bandage wrapping promotes transport of water and small molecules in the less viscid, heated tissue, and the increase in tissue hydrostatic pressure decreases net capillary filtration and hence lymph formation.

DISCUSSION

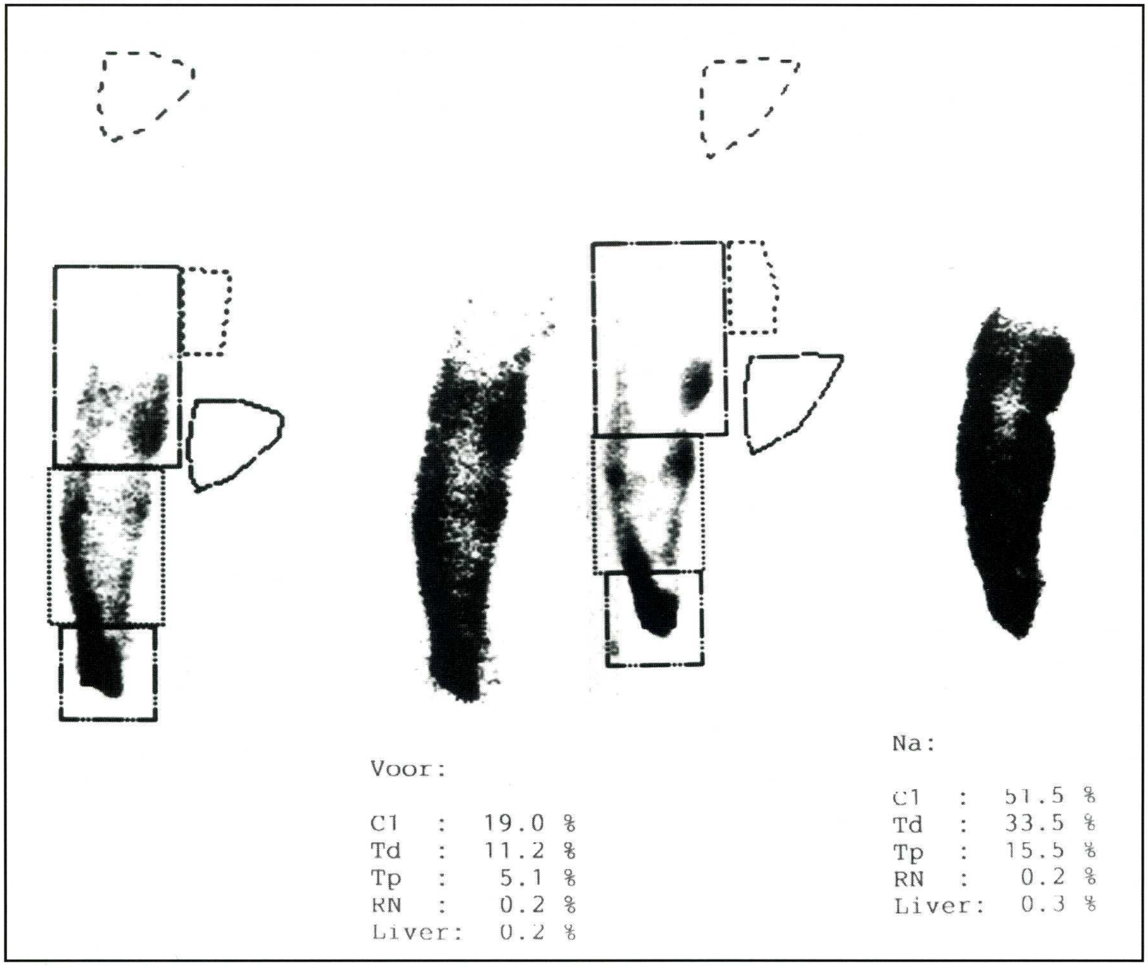

Fig. 7. C-scan of a patient with post-mastectomy lymphedema before (left) and after (right) thermotherapy. There was a dramatic increase in radiotracer clearance (Cl); however, the radionuclide did not reach the bloodstream (the activity of the liver did not change) and simply pooled in the arm. (See Fig. 1 for definition of abbreviations.)

Tracer investigations in our clinic started in 1967 to replace the tedious procedure of contrast lymphangiography (1). Initially, radioactive serum albumin was used (1) and later mercury sulfide colloid (19). In these earlier studies, time activity curves were produced of several regions. In later years, attention was directed to the evaluation of effects of various treatments which prompted the use of nanocoll. Now, a simplified method is described, which is a highly practical compromise to replace other time-consuming techniques. Three hours post-injection was found as the optimal single scintiscanning time. Others also favor this interval (5,7). A longer post-injection interval tends to cause blurring of the scanning image due to dissociation of 99m-Tc-nanocoll, and excretion of the tracer into the intestines via the liver. A 3-hour interval also allows optimal tracer transport if the patient is active.

The injection is properly done *intra*cutaneously (3,19-21) as *sub*cutaneous injection is not completely reliable. An intracutaneous injection produces a wheal and the chance of uptake in the lymph capillary system is maximized because lymphatics at this site are extensive, whereas blood vessels in the upper portion of the dermis are relatively scarce. Liver uptake immediately after intracutaneous injection is caused by factitious puncture into the venous system. Subcutaneous injection is also difficult to control; the tracer may be instilled into a fat lobule, surrounded by fibrous tissue, or into fibrous septa directly or into a blood vessel or into a dilated lymphatic capillary or lymphocele. Deposition of the radionuclide in the cutis is more reliable and under visual control.

Peripheral lymph congestion due to obstruction of epifascial lymphatics increases hydrostatic pressure in the dermal lymph capillaries producing dermal backflow. Transport of the radiopharmaceutical depends on the interstitial pressure which is increased in lymphedema (12) and which can be very high in severe edema. Sometimes radiotracer transport is negligible and only slow diffusion from the injection site occurs. If tissue pressure decreases, for instance after bedrest and limb elevation, the radiotracer clearance, i.e., disappearance of the nuclide from the injection site increases, but this finding does not signify where the tracer has gone. Accordingly, measuring clearance alone (22) may be misleading as much of the nuclide may be deposited in the distal portion of the extremity. Moreover, a slightly improved scintiscan image after operation may result from concomitant ongoing non-operative treatment such as pre- and post-operative bedrest, limb elevation, and the wearing of elastic stockings, which accompany operative therapy.

Lymph nodal uptake depends upon the nodal reticuloendothelial system and the capacity of its sinuses. If the nodes are scarred, absorption of the colloid is minimal as in primary lymphedema. If intranodal lymph vessels are also sclerosed and obstructed, no nodal activity is registered as transport through the nodes is obviated, and no liver activity is found. In this regard, the C-scan displays no difference between primary and secondary lymphedema as, for example, after a groin dissection. Lymphedema due to distal hypoplasia possibly complicated by repeated erysipelas attacks may display no radiotracer clearance (obliteration of distal lymphatics). In these instances, injection of tracer at the level of the knee may display lymphatics in the upper leg and groin. Measurements made 3 hours post-injection may seem overly static but if the patient walks around after the injection until the final scintigram is done, the tracer is cleared from the injection site and stored in several regions in different ways and quantities due to various pathologic derangements. Deposition of activity thus depends not only upon the state of the lymphatic system but also is a function of time.

The nuclide uptake in the liver derives from lymphatic transport to the bloodstream and hepatic Kupffer cell trapping. In secondary lymphedema, the capacity of the lymphatic system distal to the obstruction site (usually at the level of the regional nodes) increases due to dilatation of the lymphatic bed. Outflow of lymph from the extremity, however, is typically impaired and liver activity is minimal (<1%).

In normal extremities, liver activity depends upon the quantity of the injected dose, absorption by the nodal reticuloendothelial system and the capacity of the peripheral lymphatic system. If the recommended dose of 20 MBq is used, the amount of radionuclide in the liver is about 1% of the total body count. Tracer clearance, which represents the total amount of radioactivity which has disappeared from the injection site in 3 hours, equals the sum of the activities of all regions of interest. Besides this semi-quantitative capability, a qualitative picture or image is generated which localizes where radioactivity has accumulated. This feature can facilitate planning of operative procedures. Similarly, alternative patterns of lymph flow may be detected and visualization of unusual structures such as contralateral or

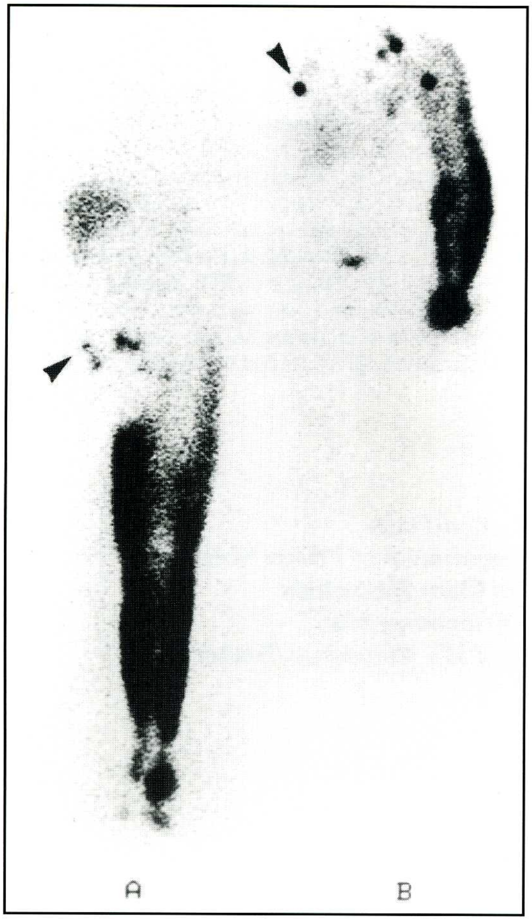

Fig. 8. A. C-scan of a man with secondary lymphedema of the left leg. An operative attempt was made to drive left leg lymph to the right side by a scrotal flap. Note the appearance of contralateral groin nodes (arrowhead) after the procedure. B. Patient with post-mastectomy arm lymphedema. Note the appearance of contralateral axillary nodes (arrowhead) before start of treatment.

remote lymph nodes may be displayed *(Fig. 8)*.

The method described has a low radiation dose hazard and affords the possibility of assessing treatment not only by clinical impression but by objective data. Using an injection dose of 20 MBq, the maximal number of counts per pixel cannot be exceeded even where no clearance occurs as in severe lymph stasis. The count rate losses (dead time), which occur in high count rates, are minimized, and the calculated effective dose equivalent for the body according to the models of the MIRD is 0.005 mSv/MBq.

Finally, as noted previously, C-scan does not disclose causation of lymphedema. Whereas most primary and secondary lymphedemas can be evaluated by C-scan, chylous reflux syndromes, which are rare, may require complementary studies.

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