OFFICIAL ORGAN
OF THE

EUROPEAN GROUP
OF LYMPHOLOGY
LATIN-MEDITERRANEAN
CHAPTER OF ISL
SOCIETÀ ITALIANA
DI LINFANGIOLOGIA

THE EUROPEAN JOURNAL OF lymphology

and related problems

VOLUME 10 • No. 37-38 • 2002-2003

INDEXED IN EXCERPTA MEDICA

SUMMARY

THE EUROPEAN JOURNAL
OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

IMAGING OF THE LYMPHATIC SYSTEM: HISTORY AND FUTURE IN ONCOLOGY

R. Musumeci, Balzarini A.°, T. De Simone*, C. Sigari°*
** Unit of Diagnostic Radiology A.*
° Unit of Rehabilitation and Palliative Care

National Cancer Institute - Milano

Fantastic and fascinating appears the hystory of recognition, description and interpretation of the functions of the third circulation, i.e. of the lymphatic system.
The first description of those strange, milk or better "similar to milk" fluid carrying vessels is due to Hippocrates (460-377 B.C.), while the first description of a dissection of the abdominal chyliferous vessels has been presented by Herophilus (300 B.C.).
After this exploit, lymphologists and Lymphology acted as "Sleeping Beauties" and no further interest was given to this argument. Even Leonardo, in spite of an unknown number of dissections, highly forbidden and persecuted at that times, and of his fantastic culture and scientific ability, did not gave in his work any sign of attention to this topic.
After about 2000 years an italian anatomist, Bartolomeus Eustachius, and a belgian student, Andreas Vesalius, presented in 1563 the first description of the thoracic duct in a horse, calling it "Vena Alba Toracica". This was indicative for the attribution of this vessel to the venous system.
Again almost 100 years elapsed and another italian glory, Gasparus Asellius, professor of Anatomy and Surgery at the University of Pavia, published in 1627 a book "De lactibus sive lacteis venis". In this book the first description of the lymphatic vessels of the intestine and the interpretation of their function to absorbe chyle and to carry it to the liver is given.
In 1651 a french student, Jean Pequet, anatomically studied the cisterna chyli, demonstrating that chyle does not flow through the liver but enters directly in to the venous system.
In 1652 Jan van Horne, professor of Anatomy in Leyden, described the thoracic duct in man as "novus ductus chyliferus" where, at the level of L1 is the confluence of intestinal vasa lactea described by Asellius.
Again in 1652, Thomas Bartholin and Olaf Rudbeck, through a separate work, were the first to identify the lymphatic as a system different from arteries and veins. Bartholin was also the first investigator who used the term "lymphatic vessels".
Anton Nuck in 1692 demonstrated the lymphatic system by injecting it with mercurial compounds. He was also able to assess the presence of valves in the lymphatic trunks, studying the one-way characteristic of the lymph flow.
Another italian glory in the demonstration of the lymphatic system, Paolo Mascagni from Siena, when only thirty-five following the method of Nuck, presented "Vasorum lymphaticorum corporis humani hystoria et ichonographia". (1787).
Only a few years after, the same results were achieved by William Cruikshank. (1790).
Then, hundred more years elapsed till Gerota's presentation (1896). A new technique of analytical demonstration of the whole lymphatic system was described, using Prussian Blue dissolved in turpentine and ether.
Using the technique described by Gerota, G.M. Tossifow (1930) and H. Rouviere (1932) published books about the complete description of the lymphatic system.

And what about radiological imaging?

The first systematic attempts for the radiological demonstration of the lymphatic network started more than 30 years after the publication of W.C. Roentgen (1895).
The method was called "indirect lymphography", i.e. the injection of contrast medium in the connective tissues, body cavities and organs. Problems were correlated with the choice of the contrast media . The use of Thorotrast for istance was dangerous for its radioactivity.
Anyway the major problem was due to the fact that the lymphatic system does not absorbe the contrast material rapidly enough to adequately and diagnostically visualize the vessels and the nodes.
The new attempt for radiographic imaging of the lymphatic system was "direct lymphography" the injection of radiopaque contrast medium in a lymph node first and then in a lymph vessel . S. Funaoka in 1929 and R. Carvalho (1931) were the fathers of direct injection of contrast medium in a node. After these first presentations, Teneff and Stoppani in Italy (1936) and M. Servelle in France (1944-45) described methods of visualization of the lymphatic channels and nodes of the abdomen, through the direct puncture of an inguinal lymph node.
Problems were correlated to the high toxicity of the dyes (mainly Thorotrast) that were employed the same difficulties were encountered by Funaoka and his group (1929), who were the first to inject a radiologically detectable contrast medium directly into a lymph vessel.

THE EUROPEAN JOURNAL
OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

IMAGING OF THE LYMPHATIC SYSTEM: HISTORY AND FUTURE IN ONCOLOGY

R. Musumeci, Balzarini A.°, T. De Simone*, C. Sigari°*
** Unit of Diagnostic Radiology A.*
° Unit of Rehabilitation and Palliative Care

National Cancer Institute - Milano

Fantastic and fascinating appears the hystory of recognition, description and interpretation of the functions of the third circulation, i.e. of the lymphatic system.
The first description of those strange, milk or better "similar to milk" fluid carrying vessels is due to Hippocrates (460-377 B.C.), while the first description of a dissection of the abdominal chyliferous vessels has been presented by Herophilus (300 B.C.).
After this exploit, lymphologists and Lymphology acted as "Sleeping Beauties" and no further interest was given to this argument. Even Leonardo, in spite of an unknown number of dissections, highly forbidden and persecuted at that times, and of his fantastic culture and scientific ability, did not gave in his work any sign of attention to this topic.
After about 2000 years an italian anatomist, Bartolomeus Eustachius, and a belgian student, Andreas Vesalius, presented in 1563 the first description of the thoracic duct in a horse, calling it "Vena Alba Toracica". This was indicative for the attribution of this vessel to the venous system.
Again almost 100 years elapsed and another italian glory, Gasparus Asellius, professor of Anatomy and Surgery at the University of Pavia, published in 1627 a book "De lactibus sive lacteis venis". In this book the first description of the lymphatic vessels of the intestine and the interpretation of their function to absorbe chyle and to carry it to the liver is given.
In 1651 a french student, Jean Pequet, anatomically studied the cisterna chyli, demonstrating that chyle does not flow through the liver but enters directly in to the venous system.
In 1652 Jan van Horne, professor of Anatomy in Leyden, described the thoracic duct in man as "novus ductus chyliferus" where, at the level of L1 is the confluence of intestinal vasa lactea described by Asellius.
Again in 1652, Thomas Bartholin and Olaf Rudbeck, through a separate work, were the first to identify the lymphatic as a system different from arteries and veins. Bartholin was also the first investigator who used the term "lymphatic vessels".
Anton Nuck in 1692 demonstrated the lymphatic system by injecting it with mercurial compounds. He was also able to assess the presence of valves in the lymphatic trunks, studying the one-way characteristic of the lymph flow.
Another italian glory in the demonstration of the lymphatic system, Paolo Mascagni from Siena, when only thirty-five following the method of Nuck, presented "Vasorum lymphaticorum corporis humani hystoria et ichonographia". (1787).
Only a few years after, the same results were achieved by William Cruikshank. (1790).
Then, hundred more years elapsed till Gerota's presentation (1896). A new technique of analytical demonstration of the whole lymphatic system was described, using Prussian Blue dissolved in turpentine and ether.
Using the technique described by Gerota, G.M. Tossifow (1930) and H. Rouviere (1932) published books about the complete description of the lymphatic system.

And what about radiological imaging?

The first systematic attempts for the radiological demonstration of the lymphatic network started more than 30 years after the publication of W.C. Roentgen (1895).
The method was called "indirect lymphography", i.e. the injection of contrast medium in the connective tissues, body cavities and organs. Problems were correlated with the choice of the contrast media . The use of Thorotrast for istance was dangerous for its radioactivity.
Anyway the major problem was due to the fact that the lymphatic system does not absorbe the contrast material rapidly enough to adequately and diagnostically visualize the vessels and the nodes.
The new attempt for radiographic imaging of the lymphatic system was "direct lymphography" the injection of radiopaque contrast medium in a lymph node first and then in a lymph vessel . S. Funaoka in 1929 and R. Carvalho (1931) were the fathers of direct injection of contrast medium in a node. After these first presentations, Teneff and Stoppani in Italy (1936) and M. Servelle in France (1944-45) described methods of visualization of the lymphatic channels and nodes of the abdomen, through the direct puncture of an inguinal lymph node.
Problems were correlated to the high toxicity of the dyes (mainly Thorotrast) that were employed the same difficulties were encountered by Funaoka and his group (1929), who were the first to inject a radiologically detectable contrast medium directly into a lymph vessel.

A major progress was obtained by J.B. Kinmouth (1954) with injection through a surgical procedure of water soluble contrast medium in a lymphatic channel in the dorsum of the foot. The contrast medium was the same as for angiography (water soluble iodized contrast such as Pyelosil).
Problems were correlated with fast visualization of the vessels but with reduced intensity as you proceed away from the injection site and faint and diagnostically insufficient opacification of the nodes.
But the way was open and different groups of investigators suggested and experienced oily contrast media such as Lipiodol F or Ethiodol. P. Malek in 1959, J. Prokopec et al. (1959), Hreschyshyn et al. (1961) and S. Wallace (1961), using oil based radiopaque contrast media, started the new era of diagnostic imaging of the lymph vessels and nodes.

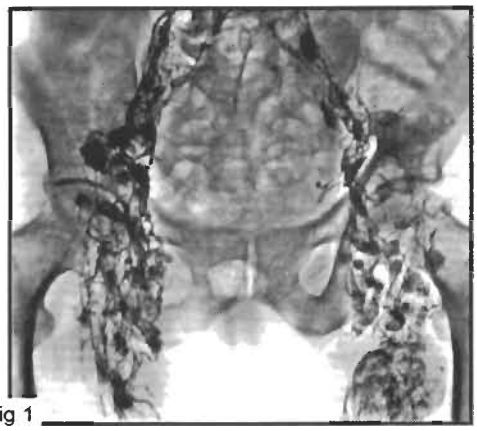


Fig 1

In **fig. 1** is shown the network of vessels in the inguino-pelvic area, opacified with Lipiodol classically injected in the dorsum of the foot.
Fig. 2 is a macrophotography of an excised lymph node after lymphography. The oily contrast medium is seen filling the internal lymph node tissue with the pattern of droplets. If the node is radiographed, the radiopaque oil droplets produce the typical appearance that, in combination with the size of the lymph node and the patency of the lymphatic channels, suggests the diagnosis.


Fig 2

In the **fig. 3** the radiographic pattern can be considered as evocative of lymph node involvement in lymphoma.
On the contrary **fig. 4** shows the typical appearance of a solid tumor metastasis. The neoplastic tissue acts in the lymph node as a foreign body which is impenetrable to the radiopaque dye.


Fig 3

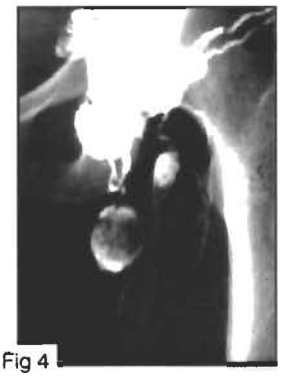


Fig 4

The metastasis appears as a filling defect and disturbances of the lymph flow are very frequent.
From that moment (1960) an exhaustive work up started, including lymphangiography (LAG) among the radiologic diagnostic procedures to assess the N parameter in patients with cancer.
The vast majority of the examinations (more than 95%) were foot lymphangiographies , due to the easier procedures and to the large lymph nodal areas (inguinal, pelvic and retroperitoneal) suitable for diagnostic exploration,. In a smaller percentage upper arm, cervical or penile lymphangiograms were performed.
In 1963 contemporaneously two differerent groups of researchers, Bush et al. in USA and Chiappa et al. in Italy, presented a new technique for the evaluation of the retroperitoneal nodes draining the lymph from the testis.


Fig 5

The procedure, a classical radio-surgical evaluation, is based on the knowledge of developmental embriology of the male gonads.
In **figures 5 and 6** a radiograph of the so called "funicolar" LAG and the radiographic combination of funicolar and foot LAG are presented. From the evaluation of these images , the following statements are possible:

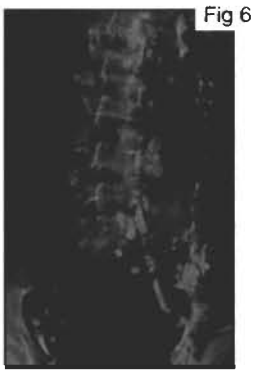


Fig 6

-male gonads drain the lymph to the high retroperitoneal area.
-the first lymph nodes are external to the lumbar retroperitoneal trunks.
-the lymphatic vessels show the internal valves and lymph flow goes exclusively in the directionfrom the testis to the nodes.
-the first lymphatic nodes can be opacified only through the funicular route.
-if the first nodes are involved, metastases are possible , even if not mandatory, also in the para-aortic area.
-if you notice metastases in the retroperitoneal area through foot LAG, you must considered also involved the first node groups.
These statements are mainly true for left sided tumors.
The standard foot LAG is not always suitable to demonstrate all the conditions of the neoplastic patology of the abdominal nodes. Radiology and radiologists suggested a group of ancillary procedures for a better and complete evaluation of the lymphatic system. We have to consider that at that times (1960-1970) no great imaging machines were available and the ancillary procedures included:
-Plain film .
-Gastrointestinal examinations.
-Contrast evaluation of the Urinary tract.

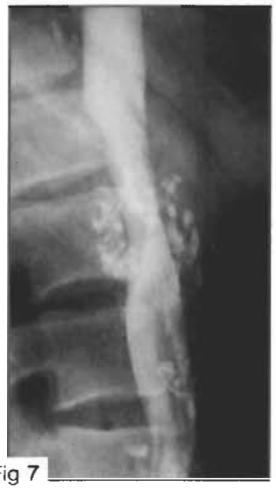


Fig 7

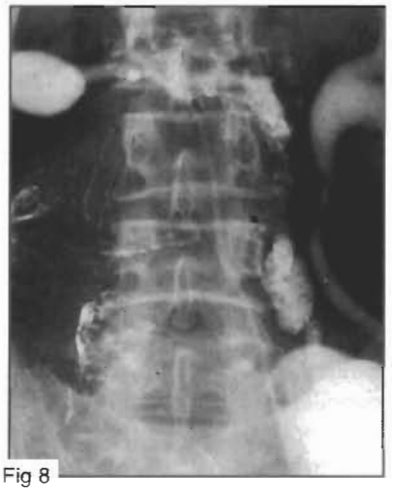
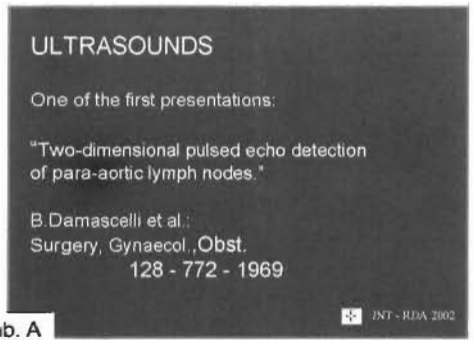


Fig 8

-Vascular procedures.

In **figures 7 and 8** a combination of inferior venocavography and intravenous pielography with LAG are reported .

The era of the imaging machines



Tab. A

This era started at the very end of the sixties with the first Ultrasounds and passing through Computerized Tomography arrived to Magnetic Resonance Imaging. The first available technology were "Ultrasounds" **(tab. A)** and one of the first (and probably the first published on an International Journal) presentation was that of an Italian group of radiologists.

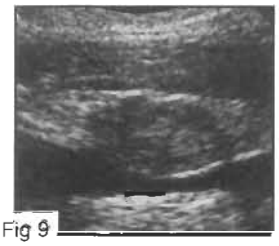
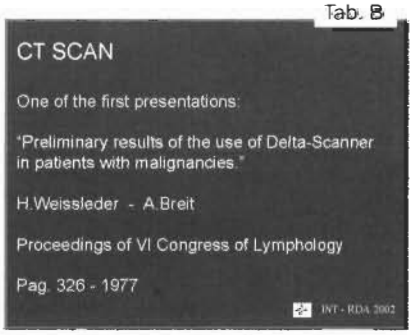


Fig 9

After the initial difficulties, today the tool is widely available, fast, cheap and with good diagnostic possibilities **(fig. 9)**. The second tool, according to the time of availability and not to importance, is CT **(tab. B)**.

Tab. B



The first presentation during the VI International Congress of Lymphologhy (1976) was dedicated to the evaluation of the lymph node areas in patients with cancer for staging. Today the tool is the most important imaging procedure to assess the conditions of the lymph nodes, independently from the site of presentation **(fig. 10 and 11)**.

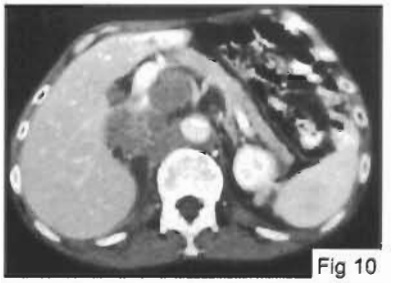


Fig 10

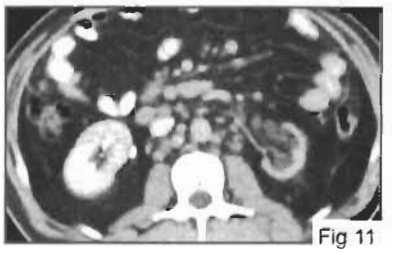


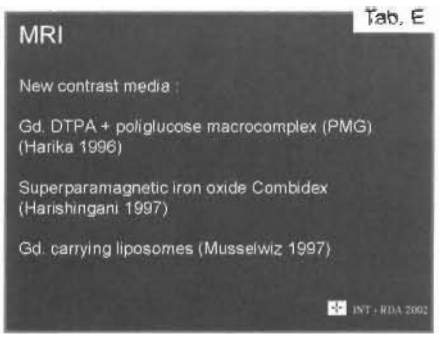
Fig 11

CT is also adequate in the evaluation of swollen limb, with the aim to differentiate the following clinical situations:

-Fat limbs;
-Lymphoedema;
-Phleboedema;
-Mixed pattern.

The diagnosis is possible with post-processing, through measurement of the subcutaneous soft tissue thickness, of the area of the muscular surface and of the area of the whole thigh. Fat leg shows only a simmetrical enhancement of the thickness of the subcutaneous fat, while lymphoedema is characterized by an enhancement of the subcutaneous fat with normal muscular area and phleboedema shows normality of the subcutaneous fat and enlarged muscular area.

Tab. E



The last imaging machine is the Magnetic Resonance Scanner. The first presentation of images of the retroperitoneal lymph nodes **(tab. E)** was performed by R. Musumeci from Italy at the ISL Congress of Lymphology in Adelaide (1985), **(fig. 12)**.

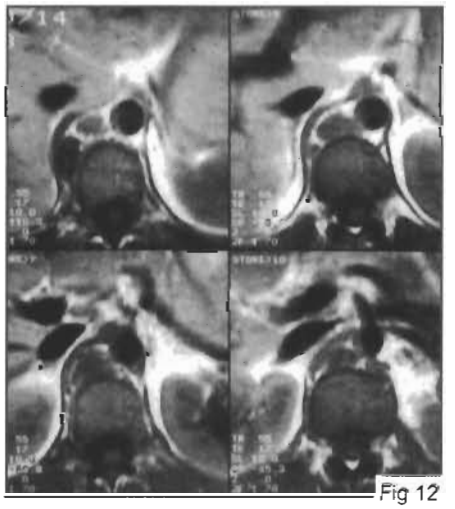


Fig 12

Now the tool, initially considered as inadequate and expensive, with or without paramagnetic contrast is widely used all over the world.

Again one of the first presentations on a journal quoted on Index Medicus is due to an Italian young researcher, who in 1986 published on "La Radiologia Medica" a paper "Study of adenopathies: what is the current role of Magnetic Resonance?"

MRI is also adequate, with maybe better image quality, in the

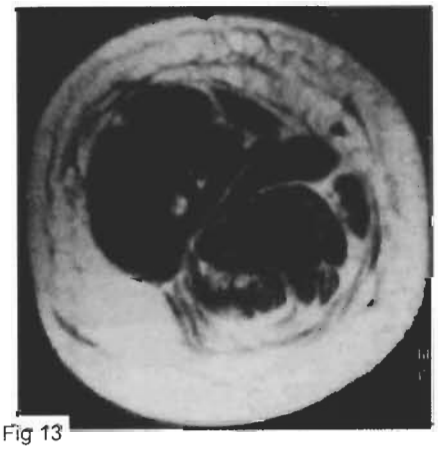


Fig 13

evaluation of the swollen limb.
The first images (**fig. 13 and 14**) were presented at the ISL Congress of Lymphology in Vienna in 1987 by R. Musumeci.
Fig. 13 shows a typical lymphoedema and **fig. 14** a very characteristic pattern of phloeboedema.

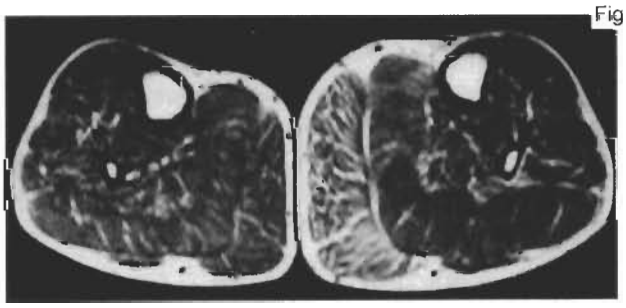
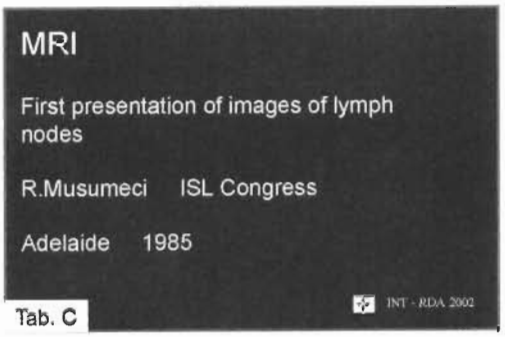


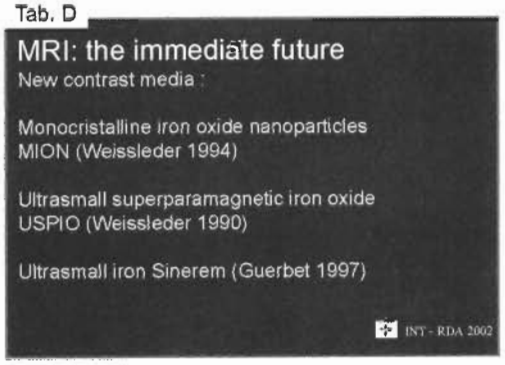
Fig 14

It is also possible to hypotize the immediate future of MRI. The diagnostic improvement can be achieved not only in new hardware and software of the machine, but in the development of new specific contrast media. **Tables C and D** report a summary of the Author and the year of first presentation od these dyes.



Tab. C

Tab. D



This attitude to develope new contrast media represent a great hope for new diagnostic possibilities in investigatiors.

Anyway not always a new contrast represents a significant diagnostic improvement. For istance a number of years ago, a new water soluble , radiopaque contrast medium was developed by Schering for indirect LAG. But, while the dye was adequate in the evaluation of the terminal lymphatics in patients with peripheral lymphoedema using also direct Radiographic magnification, the results were not so exciting in oncology.

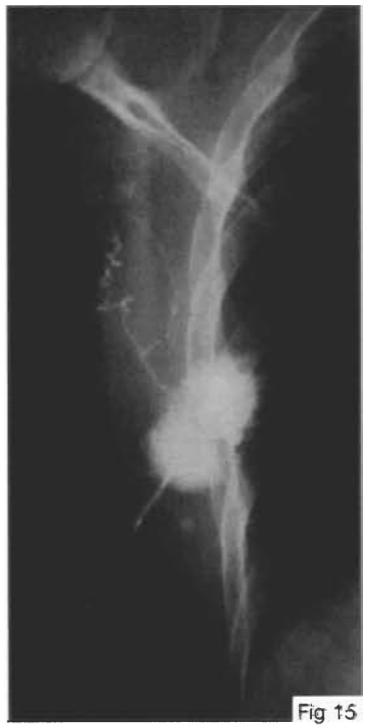


Fig 15

In a classical oncologic "court" as breast cancer, the problems of axillary lymph nodes and the decision if axillary dissection must be considered as optional or mandatory, was and is a very important choice, both for diagnostic and prognostic purposes. In Tab. F a paper from R. Musumeci et al. from Italy (1984), suggests how the new contrast is unable to achieve a complete evaluation of the axillary lymph nodes.
The dye is inadequate for oncologic purposes because it allows a good evaluation of the vessels but not of the nodes **(fig. 15)**.
The diagnostic problem has been solved by means of the evaluation, through medico-nuclear tecniques, of the so called sentinel lymph node. But is easily understandable why Musumeci et al. presented their experience as a "vanishing hope". And what is the imaging direction for the immediate future? The future of imaging lymph nodes in patients with cancer could be identified in a combination of tools such as MRI or CT + PET or in a more simple tecnique of image fusion. In **(fig. 16 e 17)** are reported an MRI and a PET image of the same patients with stage III Hodgkin's Lymphoma.
Through these tools a combination of morphological and functional imaging procedures can be archieved.

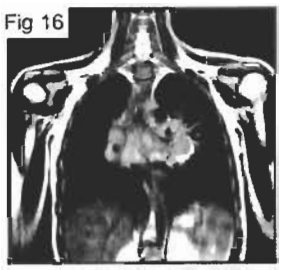


Fig 16

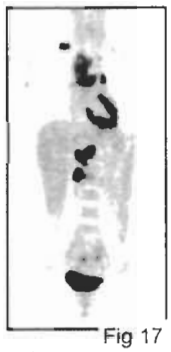


Fig 17

REFERENCES FOR CONSULTATION
1.Clouse M.E.: Clinical Lymphography
William and Wilkins Ed. - Baltimore 1977
2.Kinmonth J.B.: The Lymphatics
Arnold Ed. - London 1972
3.Kuisk H. : Technique of lymphography and principles of interpretation .
Green H.W. Ed. - St. Louis 1971
4.Molander D.W.: Diseases of the lymphatic system
Springer-Verlag Ed. - New York 1984
5.Musumeci R. - Mauri M. : La linfografia in oncologia
Ilford Ed. - Origgio 1980

THE EUROPEAN JOURNAL
OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

DISABILITY AND LYMPHEDEMA: WHICH FUNCTIONAL SCALE TO DETERMINE THE 'NECESSITY OF ASSISTANCE'?

Michelini S., Failla A., Moneta G., Macaluso B.
S. G. Baptiste Hospital . A.C.I.S.M.O.M. Rome - Italy
e-mail : wcmmic@tin.it

KEY WORDS : Lymphedema, disability.

SUMMARY :

In the various clinical stages Lymphedema determines various levels of disability, both physical as psychological; and is a cause of different stages of 'necessity of assistance' in the patient.
The Aim of the study is, using the F.I.M. scale (functional indipendence measure), to define the degree of 'necessity of assistance' (necessity of assistance, either direct by other person or indirect, by means predisposition of aids, to carry out the activity daily life) for patients suffering from lymphedema in various clinical stages and to point out the physical improvement after the treatment.
112 patients (69F and 43M) were studied, age ranging from 32 and 77 years old, who suffered from primary or secondary lymphedema of the limbs (46 of the upper limbs - 4 bilateral, and 66 of the lower limbs - 21 bilateral), at different clinical stages (from I to V).
The F.I.M. scale (functional independence measure) was used before and after physical combined treatment for each patient. Before the treatment over 73% of subjects don't were 'self-sufficient' and about 18% required a moderate or intensive assistance.
After the treatment subjects gained from 1 to 3 levels in the disability scale with corresponding 'assistance necessity'. So, the use of this scale allows to quantify the results of the combined treatment from functional aspect.
The AA. Conclude that Lymphedema , in clinical stages more advanced determine more 'assistance necessity' in the patients; the degree of the assistance decreases after the treatment, above all in II and III clinical stages.

INTRODUCTION

Lymphedema cause psychological and physical disability and can reduce, in some kinds (II, III, IV, V clinical stages), the functional capability of the diseaded patients more than a stroke or an ischemic heart pathology.
It's difficult to determine the various levels of 'assistance necessity' because the various scales used to define the parameters of disability don't are not frequently universally acceptable. So, in various scales (F.I.M., Barthel, 8,9) the proposed items reveal themselves not completely appropriates to the kind of pathology (for exemple some informations on sphinteric function or on memory of the subjects).
The F.I.M. scale (9) is the most used to define the majority of functional disabilities determined by the various pathologies that determine handicaps. It's still today generally valid that the F.I.M. principle-scale, in function of the disability induced by a pathology, identifies the various levels of 'necessity of assistance', eventually reversible by means the different tailored treatments applied in every case.
The Aim of this work is, using the F.I.M. scales, to quantify the degree of 'necessity of assistance' in patients suffering from lymphedema in basal condition and after the treatment (as a function of the clinical stage of the lymphedema) and to analyze the improvement of the patients' functional conditions after treatment (as a function of the clinical stage of lymphedema as a function of the degree of 'necessity of assistance' in basal conditions).

PATIENTS AND METHODS

112 patients (69 women and 43 men: age ranging from 32 and 77 years old) who were suffering from primary (n=54) and secondary (n=58) lymphedema were studied.
They were subdivided, as function of the clinical stage (10), in the following 5 groups:
- Clinical stage I (subclinical in risk subjects; either, mastectomized with coinciding limbs, or subjects with blood relation with patients suffering from primary lymphedema and positive lymphoscintigraphic exam): 11 women, all with upper limbs lymphedema (all monolateral), age ranging from 27 and 79 years;
- Clinical stage II (presence of oedema that spontaneously decreases with bed-rest): 18 women and 10 men, age ranging from 26 and 81 years, 12 with upper limb lymphedema (1 bilateral) and 16 with lower limbs lymphedema (11 bilateral);
- Clinical stage III (presence and persisting of oedema that decreases only by means physical and/or pharmacological and/or microsurgical treatment); 27 women and 23 men, age ranging from 34 and 82 years, 14 of which with upper limb

lymphedema (1 bilateral) and 35 with lower limbs lymphedema (7 bilateral);
- Clinical stage IV (elephantiasis with disappearance of bony and tendon relieves); 9 women and 8 men, age ranging from 37 and 78 years, 7 with upper limbs lymphedema (monolateral in all) and 9 with lower limbs lymphedema (2 bilateral);
- Clinical stage V (elephantiasis with associated ulcers, dermoipodermitis, muscular hypotrophy and articular damages); 4 women and 2 men, age ranging from 53 and 75 years, 2 with upper limbs lymphedema (monolateral in the 2) and 4 with lower limbs lymphedema (bilateral in all).

All the patients underwent to tailored physical training (M.L.D. for stage I; M.L.D. with sequential pressotherapy, isotonic gymnastic under elasto-compressure for other clinical stages). At the end of the treatment (10 sessions) one definitive elastic garment was prescribed.
The F.I.M. scale was applied before and after the treatment. It is founded on the evaluation on 18 items concerning the following aspects: self-care, sphinteric control, mobility, locomotion, communication capability, relational capability and cognitive capability. Each item is scored from 1 to 7.
The 100% of patient's ability corresponds to a score of 126 (7 X 18)/ 126.
In function of the total score, 7 different levels are identified in relation to 'necessity of assistance':
- Level 7 = complete self-sufficiency;
- Level 6 = self-sufficiency with adaptations;
- Level 5 = Supervision/predisposition by other people to consent to
the subject to be self-sufficient for the primary and secondary needs;
- Level 4 = low level of assistance;
- Level 3 = moderate level of assistance;
- Level 2 = intensive level of assistance;
- Level 1 = total assistance (total disability).
The items are 18; so 18 (items) X 7 (levels) = 126. 126 points correspond to complete self -sufficiency (100%).

RESULTS

In basal conditions patients demonstrated the following total levels in relation to the clinical stage (see table 1):
- **I stage:** all the patients demonstrated the level 7;
- **II stage:** 1 patient level 7, 16 patients level 6, 12 patients level 5
- **III stage:** 2 patients level 6, 17 patients level 5, 28 patients level 4, 2 patients level 3;
- **IV stage:** 1 patient level 6, 2 patients level 5, 2 patient level 4, 11 patients level 3, 1 patient level 2;
- **V stage:** 1 patient level 4, 3 patients level 3, 2 patients level 2.

Stage/FIM class/level	Before treatment							
	1	2	3	4	5	6	7	Total
I							11	11
II				8	7	12	2	29
III			2	28	17	2		49
IV		1	11	2	2	1		17
V	1	1	1	2	1			6
Total	1	2	14	40	27	15	13	112

Tab I F.I.M. scale levels in patients in basal conditions

Stage/FIM class/level	After treatment							
	1	2	3	4	5	6	7	Total
I							11	11
II					6	9	14	29
III				16	12	20	1	49
IV			5	4	4	3	1	17
V				2	3	1		6
Total			5	22	25	33	27	112

Tab II F.I.M. scale levels in patients after treatment

After treatment, the results of the F.I.M. evaluation are given in Table 2.
Whereas one total assistance up to a moderate level of assistance was necessary in basal conditions, only five (4,1%) needed the same levels of assistance after treatment.
In the clinical stages from II to V, after the treatment, we noticed a reduction from 1 to 3 levels compared to basal values (above all in II and III clinical stage).

Table III gives the improvement of the patients' 'necessity of assistance' in function 1° of the clinical stage of the lymphedema and 2° of the level before treatment.
These two tables allow also the following comments :
- All patients but the clinically staged II were improved after treatment by at least 1 level of assistance (21,4%);
- The gain of level assistance was 2 in 52 cases (46,4%) and 3 in 25 (22,3%).

		Total
I DAN =	0	11
	1	0
	2	0
	3	0
II DAN =	0	0
	1	6
	2	15
	3	8
III DAN =	0	0
	1	10
	2	26
	3	13
IV DAN =	0	0
	1	5
	2	8
	3	4
V DAN =	0	0
	1	3
	2	3
	3	0
TOTAL DAN =	0	11
	1	24
	2	52
	3	25

Table III: Improvement of the patients 'necessity of assistance' (DAN) in function 1° of the clinical stage of the lymphedema and 2° of the level before tratment

DISCUSSION AND CONCLUSIONS

It's difficult to determine the various levels of 'necessity of assistance' in patients suffering from lymphedema because the various scales used to define the parameters of disability are not universally accepted.

So, in various scales (F.I.M., Barthel, 8,9,) the proposed items reveal themselves not completely appropriates to the kind of pathology (for exemple some informations on sphinteric function or on memory of the subjects).

Although it might be not completely appropriate to describe the lymphedema, the F.I.M. scale (9) is the most used to define the majority of functional disabilities determined by the various pathologies that determine handicaps. It is still today generally valid that the F.I.M. principle-scale, in function of the disability induced by a pathology, identifies the various levels of 'necessity of assistance' eventually reversible by means the different tailored treatments applied in every case.

Nevertheless, the functional evaluation of patients with lymphedema means the F.I.M. scale gives the following informations in our study :

- *the degree of 'necessity of assistance' in basal conditions;*
- *the improvement of self-sufficiency of the patient after combined treatment;*
- *the monitoring of functional results in the time.*

Of course we verified an apposite proportionality between the clinical stage of lymphedema and the functional capacity level according to the F.I.M. scale. We didn't observe differences in the first clinical stage. On the contrary, from II to V stage, in the majority of cases we observed an increase of functional capability of each subject with consequent reduction of the degree of 'necessity of assistance'. This improvement corresponded with an increase of final scores of the F.I.M. that, usually, fluctuate between 1 and 3 levels (in the most important cases It does not appear as such following the presented results) according to the F.I.M. scale. The improvements more important, of course, are obtained in the first clinical stages (II and III stages) (see you the Tab. I and Tab II). The study demonstrates that the disability determined by the lymphedema And the improvement of the functional capability after the treatment can be quantified. The Authors set themselves to improve the items to better adapt them to the lymphatic pathologies (with introduction in the scale also of the psychological and behavioural aspects induced by lymphedema) to make the 'evaluation scale' reproducible, valid under statistic point of view and worldwide acceptable. The Authors want nevertheless to maintain the principle of 'reduced ability' corresponding to the various levels of 'assistance necessity', determined in the F.I.M. scale: it's most important to quantify the results of the combined treatment.

REFERENCES

1) Weiss J.M., Spray B.J.: The effect of complete decongestive therapy on the quality of life of patients with peripheral lymphedema. Lymphology 35,2; 46-58. 2002;

2) Pereira De Godoi J.M., Braile D.M., Fatima De Godoi M., Longo O. : Quality of life and peripheral lymphedema. Lymphology 35,2: 72-75. 2002;

3) Casley Smith J.R. : Alterations of untreated lymphedema and its grades over time. Lymphology 28 (1995). 174.

4) Tobin M.B., Lacey H.J., Meyer L. : The psychological morbility of lymphedema. Cancer 72 (1993). 3248.

5) Michelini S., Failla A., Moneta G., Barbato N. : Proposal of evaluation of disability in patients suffering from lymphedema. European Journal Of Lymphology and related problems Vol 6 Sp Co I, 20, 1996; Abstract;

6) Lannois R., Alliot F. : A specific quality of life scale in upper limb lymphedema : the ULL-27 questionnaire. European Journal of Lymphology and related problems. Vol IX (33), 24, 2001; Abstract.

7) Corda D., Monticane M., Moschi A., Failla A. : Rehabilitations procedure for patient with limb lymphedema. Our proposal : from project to rehabilitative program. European Journal of Lymphology and related problems; Abstract;

8) Haigh R., Tennant A., Sorensen F.B., Grimby G., Marincek C., Philips S., Ring H, Tesio L., Thonnard J.L. : The use of outcome measures in physical medicine and rehabilitation within Europe. Journal Rehabil Med 2001; 33:273-278;

9) Tesio L., Granger C.V., Perucca L., Franchignoni F.P., Battaglia M.A.,Russel C. The F.I.M. Instriment in the United States and Italy. Am. J. Phys. Med. Rehabil. Vol 81, n°3, 168-176;

10)Michelini S., Failla A.: Linfedemi. Inquadramento diagnostico clinico e strumentale. Minerva Cardioangiologica. 1997. 45 Suppl. I al 6°: 11-15.

THE EUROPEAN JOURNAL
OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

SUPERFICIAL LYMPHATIC DYSPLASIA: SURGICAL TREATMENT

Raul Mattassi, Massimo Vaghi, Franca Abbritti
Department of Vascular Surgery, "G. Salvini Hospital", Garbagnate Milanese, Italy

INTRODUCTION

Vascular malformations are inborn errors of vascular morphogenesis that may affect arteries, veins or lymphatics. Only one type of defect or different combinations are possible. Lymphatic pure defects may concern main ducts or manifest as areas of dysplastic lymphatic tissue localzed anywere with little connection with main lymphatic trunks.
According to classical approach to lymphatic disease, the majority of clinical forms were included in the big chapter of "lymphedema", with the distiction between "primary" and "secondary" (1,2). This is a clinical approach without a clear anatomopathological distiction that helps to understand better the defect. In order to better understand the different types of vascular malformations, and by the way also lymphatic malformations, a new classification has been proposed during a international meeeting held in Hamburg (Germany) in 1988.
A group of international vascular experts, leads by Stefan Belov from Bulgaria, meeets together and agree to classific the vascular defects according to anatomopathological defects and not according to symptoms (see lymphedema) or in "syndromes" (see Klippel-Trenaunay syndrome between many others) that only puts together different clinical pictures (3).
This new classification divided lymphatic pure defects in TRUNCULAR and EXTRATRUNCULAR forms, according if the defect is on the main trunks (aplasia, hypoplasia or dilatation) or if the defect is characteryzed by areas of dysplastic lymphatic tissue sited outside the main trunks (fig. 1 - 2 - 3 - 4 - 5 - 6 - 7).
Embryogenesis of lymphatics is still today not well known but the majority of authors agree that lympatics has a common origin with blood vessels from the mesenchima (4). Angioblasts in the embrio forms a primitive net and, by a process of vacuolization, the primitive capillary network of Sabin and Woolard appears (5, 6).
This is the so-called "retiform stage". In a second phase, some areas of primitive capillaries regress and disappear, others remain as definitive capillaries and still others grow and develop to definitive main vessels ("troncular stage"). According to the moment of pathogenic effect the malformation will be expressed in different forms. If the pathogenetic factor acts during the retiform stage, some primitive capillaries will not regress and originate an area of dysplastic tissue sited outside the main vessels. For lymphatics, this forms are called classically "lymphangiomas" or, if diffuse, "lymphangiomatosis"; according to Hamburg classifications they are called "extratruncular malformations", limited or infiltrating. These forms has nothing to do with lymphedema.
Pathogenetic effect during truncular stage will produce a defect of main vessels with aplasia, hypoplasia or dilatation. These defects in lymphatics produce lymphedema.
Because of the common origin of al vessels, it is frequent to have combined defects.
In case of lymphatic malformations, often venous or arteriovenous defects coexist; these are the so-called "hemolymphatic defects" (2, 4) .

DIAGNOSTIC METHODS

Modern diagnostic of vascular malformations has proved that it is impossible to recognize precisely a angiodysplasia by only clinical examination. The classification of Hamburg is useful as a guide to understand the pathology. Mattassi has described the "four points" as a goal of the diagnostic process in order to get to a complete diagnosis.
The goals of the diagnosis are to establish:
- type of the defect
- site of the defect and connextion with surrounding tissues
- qualitative and quantitative hemodynamics ("what kind of flow and how much?)
- secondary effects on other tissues or organs (7, 8)

To recognize the type of the defect lymphoscintigraphy (fig. 3) and lymphography (fig 1 - 2) are the best tests. To recognize combined defects, phlebography and arteriography are necessary. To study site of the defect and connections with other tissues, MR an CT contrast enhanced are the most useful examinations (fig. 5 - 7)
To get qualitative and quantitative data of the hemodynamics of the defect, angioscintigraphy with flow curves, labelled microsphere's test and Doppler analog tracing are the most used tests Secondary effects of angiodisplasias are studied by x-rays f the bones, echocardiography and chest x-rays.

SURGICAL TREATMENT

In this paper we will discuss the treatment of extratruncular lymphatic defects, pure or combined,according to our experience. As said before, this defects may be limited, that means

with a clear limit from surrounding tissues, and infiltrating, with a diffuse interconnection with normal structures.
The most effective procedure is the resection "en bloc", that means a complete avulsion of the dysplastic area.
This procedure is possible mainly in limited defects, sited superficially (fig. 8) or in a tissue that is easy to approach (9). Upper and lower limbs are the most frequent sites (fig. 9 - 10). Sometimes collegial work with other specialists is necessary to get the best result (fig. 11).
In cutaneous lymphatic malformations a good alternative to surgery is laser treatment.
Infiltrating malformations may be a difficult problem for surgery. Treatment is performed by stages with many partial resections. The aid of ne-yag laser to perform the resection has revealed useful to prevent postoperative lymphorrhea (10). Plastic surgeon is often necessary to perform a correct and complete skin coverage of the resected area (fig. 12).
The cases of combination with other vascular malformations, like venous or arteriovenous, are a different problem.
Mainly the other defects are treated primarily because lymphatic associated malformation offers the lesser disconfort. In other cases, the resections were done including all dysplastic tissue together. Alternative to surgical treatment is the percutaneous sclerosis. Different substances has been used (bleomycine, absolute alcohol, doxycycline, OK T3) but definive results are till now not well known due to the small group os cases treated till now (11).

RESULTS

It is difficult to report about results in treatment of lymphatic malformations for several reasons.
First: in groups dealing with vascular malformations, lymphatic defects are relatively rare.
Malan (1974) reported about 42 cases with only 5 treated surgically.
Belov (1985). described 21 cases with 10 surgically procedures, mainly in hemolymphatic defects.
Our casuistic is acually of 12 surgical cases, in a group of about 1000 vascular malformations of all types; that means a incidence of 2% of lymphatic dysplasia treated surgically.
Second: they are extremely variable; that means no case is similar to another, making comparision impossible.
Third: the site and extension is also variable; in fact lymphatic dysplasias may exist in almost all tissues.
For this reasons, reported results include small groups of very different cases making general concepts difficult to obtain.
Limited defects in our experience (8 cases) have a good result with high incidence of healing if a resection "en bloc" is perfomed, although there is stil a recurrence possibility even if the resection may seem radical.
Infiltrating malformations (4 cases) may not cure but the tactic of staged limited surgical resection, laser aided, gives a signifiant improvement in life quality to the patient.

CONCLUSIONS

Lymphatic malformations are relatively rare.
They need a precise diagnostic study for a complete comprehension of the defect. The Hamburg classification and the "four points" are important guidelines for the diagnostic procedure.
Surgery is a important choice and offers good possibility to improve life quality.

REFERENCES

1) Allen, E.V. (1934): Lymphedema of the extremities. Classification, etiology and differential diagnosis. A study of three hundred cases. Arch Intern Med, 54: 606
2) Williams, H.B. (1990): Vascular neoplasms. Clin Plast Surg, 7: 397-411
Belov, St., Loose, D.A, Muller, E.: "Angeborene Gefaessfehler". (1985) Reinbeck: Einhorn Presse Ed.
3) Belov, St.: "Anatomopathological classification of congenital vascular defects". (1993) Seminars in Vasc Surg, 6 (4): 219 - 224
Malan, E.: "Vascular Malformations (Angiodysplasias)" (1974) Milan, Carlo Erba Foundation
4) Bastide, G., Lefebvre, D., Jaeger, J.F.: "The organogenesis and anatomy of vascular malformations" (1990) Int Angiol 9 (3), 137 - 140
5) Sabin, F.R.: "Origin and development of the primitive vessels of the chick and of the pig". (1917) Cont Embriol Carnegie Inst 6-7, 71
6) Woolard, H.H.: "The development of the principal arterial system in the forelimb of the pig" (1922) Cont Embriol Carnegie Inst 14, 139 -141
7) Mattasi, R.: "Surgical treatment of congenital arteriovenous defects" (1990) Int Angiol 9 (3) 196 - 202
8) Mattassi, R.: "Differential diagnosis in congenital vascular-bone syndromes". (1993) Seminars in Vasc Surg 6 (4): 233 - 244
9) Servelle, M.: "La lymphangectomie superficielle totale" (1947) Rev Chir (Paris) 66: 294
10) Landthaler, M., Hohenleutner, U.: "Laser treatment of congenital vascular malformations" (1990) Int Angiol 9 (3) 208 - 213
11) Witte, C.L., Witte, M.H., Unger, E., et al. : "Percutaneous sclerosis or excision of lymphangioma/lymphangiectasia syndromes" (1998) Lymphology 31 (suppl) 396 - 399

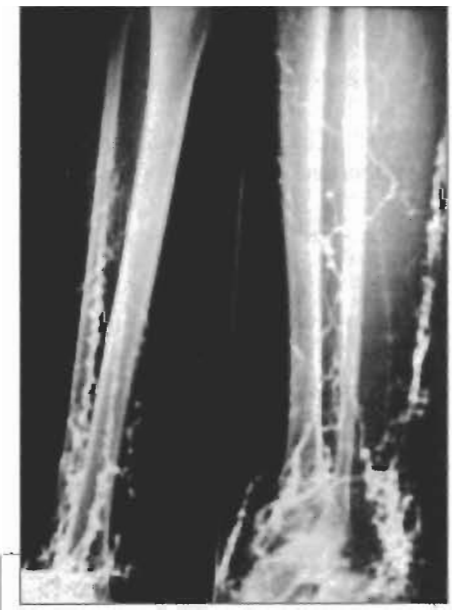


Fig. 1:
Lymphography.
Dilated lymphatic trunks. Troncular form

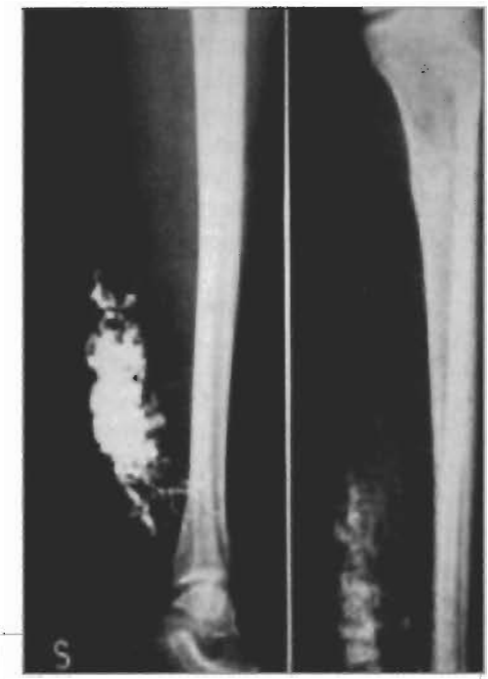


Fig. 2:
Lymphography: area of dysplastic Lymphatics.
Extratroncular form

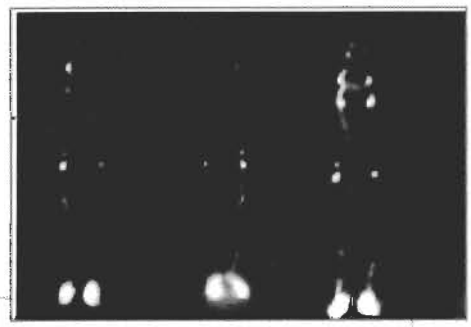


Fig. 3:
Lymphoscintigraphy.
Area of dysplastic lymphatics (arrow).
Extratroncular form.

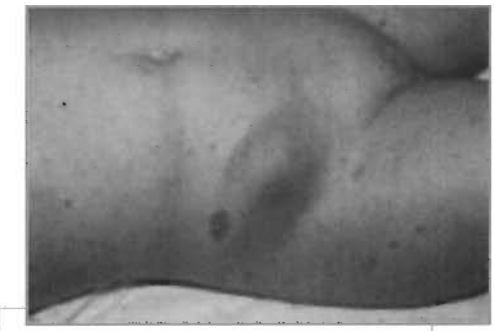


Fig. 4: Limited lymphatic malformation

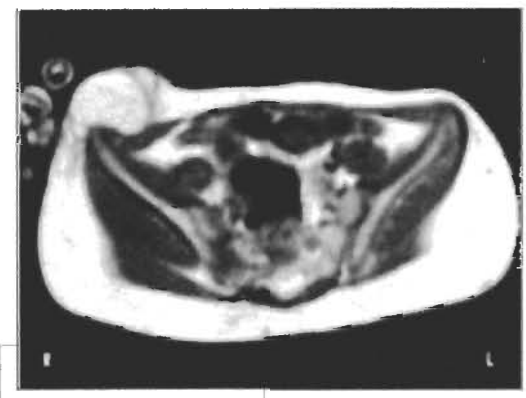


Fig. 5:
RMN of case in fig. 4

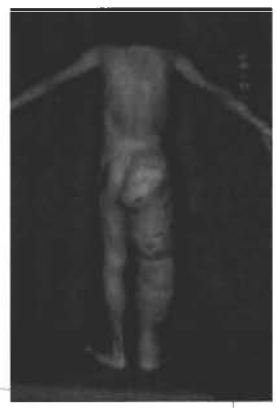


Fig. 6:
Infiltrating lymphatic malformation

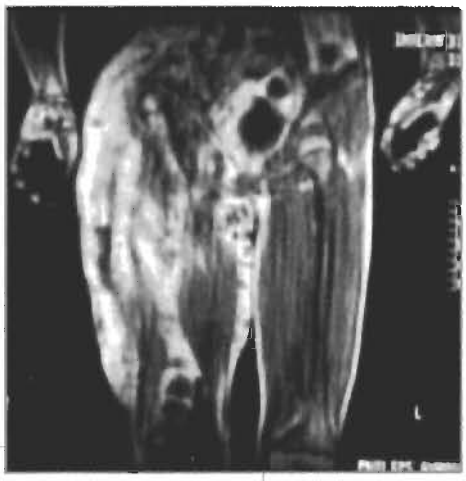


Fig. 7:
RMN of case in fig. 6

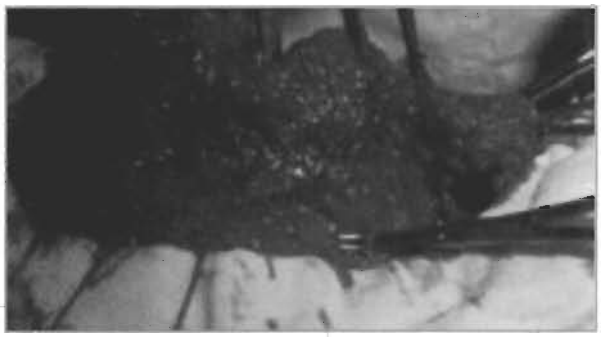


Fig. 8:
Superficial lymphangiectomy

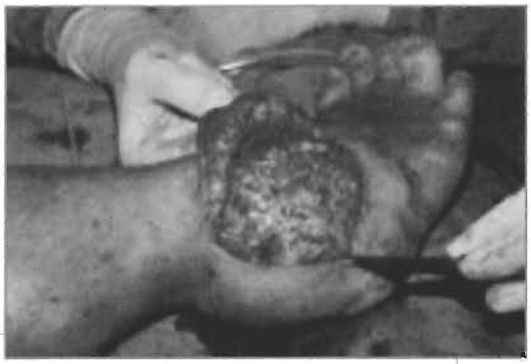


Fig.9:
Resection of superficial dysplastic lmphatics

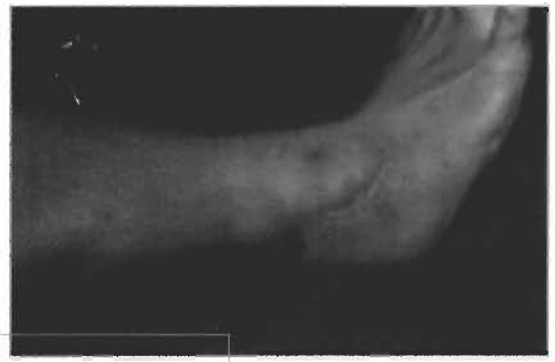


Fig. 10:
Results of surgery

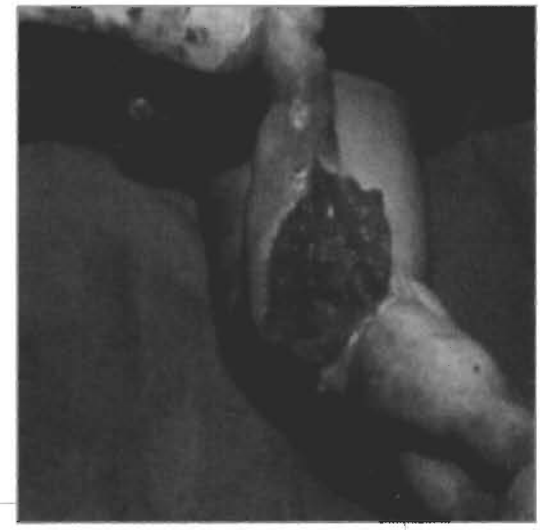


Fig.11:
Operation together with hand surgeon
Multidisciplinar approach

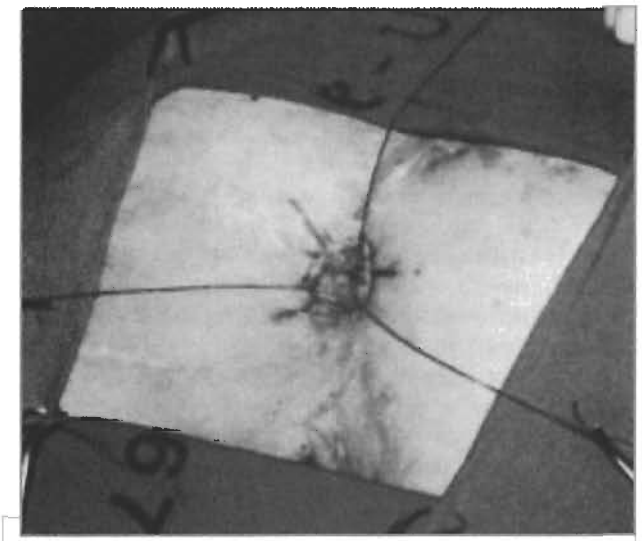


Fig. 12:
Perineal lymphatic malformation: Surgical treatment together with plastic surgeon

THE EUROPEAN JOURNAL OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

MICROCIRCULATION VARIATIONS DURING LYMPHEDEMA

Docteur A.DURAND, Professeur G. THIBAUT
Faculté de Médecine de Nancy
9 avenue de la Forêt de Haye
Boite postale 184
54505 Vandoeuvre -les - Nancy Cedex - FRANCE

ABSTRACT

The Authors studied 23 subjects suffering from monolateral lymphedema of the limbs.
All the patients underwent to lymphoscintigraphic exam that confirmed the clinical diagnosis.
The authors performed a laserdoppler exam of two limbs in comparison. In affected limbs the study emphasized that the storage capacity of blood has decreased because of lymphoedema.
The results could be compared with those obtained with venous pletismography. The decrease of storage capacity was proportional to the volume of lymphedema.

KEY WORDS: Microcirculation alterations. Lymphedema.

I INTRODUCTION

Liquid accumulation in the interstitial tissue induce oedema. An organo-mechanical insufficiency of lymphatic drainage induce liquid accumulation coming from blood vessels, in interstitium, making lymphedema [2] [7] [10].
The purpose of the experiment is to study, with doppler laser instrument [11], the microcirculation modifications induced by lymphedema.

II MATERIAL AND METHODS

- Patient
For this study , we did not resort to healthy volunteers. The selected patients have a unilateral lymphedema of inferior limb. The doppler laser study was included in a systematic check-up carried out before lymphedema treatment . All patients have given consent. Studied patients are aged 49 to 68 years. Mean age is 54 years. The population is composed with 11 men and 12 women.
Clinical diagnosis of lymphedema was sure, but lymphoscintigraphy were performed to confirm the lymphedema disease. Only patients with unilateral lymphedema of a single limb were investigated . Bilateral lymphedema were excluded of the study.

- Laser doppler
To study microcirculation, we use a laser doppler (Moor Instrument type Mbf3) enabling us to record 3 parameters ; velocity, concentration and flux of the blood cells [3],[4]. Each parameter is measured each 2,5 hundredth of second. To have an optimum exploitation of the thousands data obtained during each recording , laser doppler is connected to a computer. The data are analysed with a program provided by Moor Instrument.

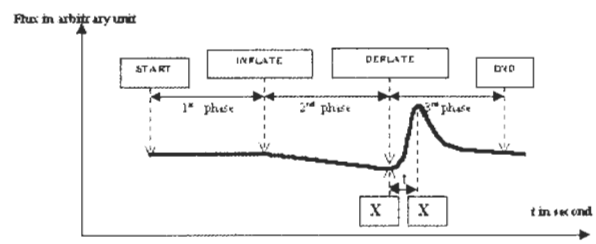
- Principle of the study
The laser probe is placed on the skin in front of the interval between 1st and the 2nd metatarsus. The probe does not study one capillary only, but a group of capillaries located in a constant, subcutaneous volume of tissue determined by apparatus characteristics. In these conditions, it is impossible to compare the results of 2 recordings on the same patient and on 2 different patients . In order to compare recordings , we use a venous tourniquet positioned on the thigh of the limb under investigation. We study and we compare the microcirculation variations while the tourniquet is inflated and deflated.

- Procedure
1. Probe is placed on the skin in front of the interval between 1st and 2nd metatarsus.
2. The venous tourniquet composed of an inflatable muff is placed on the thigh of explorated limb; it is inflated automatically to obtain 50 mm Hg pressure able to stop back circulation. This 50 mm Hg pressure is maintained during 4 minutes. Using an automatic instrument allows us to assert that the action of the tourniquet is the same for all explorations.
3. Flux F is investigated following 3 steps (fig. 1)
* In the first 3 minutes :tourniquet is deflated, we study base microcirculation.
* The tourniquet is inflated to 50 mm Hg pressure during 4 minutes.
* The tourniquet deflates automatically, and the measurement goes on during 3 more minutes
4. For each patient, a doppler laser investigation is carried out on the limb with lymphedema but also on controlateral leg which is used as control.

III RESULTS AND STATISTICAL STUDY

RESULTS
The study was carried out on 23 patients. For each patient, the laser doppler exploration was carried out on both legs in the same conditions. All curves obtained have the same shape for all explored legs (with and without lymphedema). Figure 1 qualitatively shows a typical blood capillary curve.

figure 1



For all patients, the first 2 phases are comparable, but we note an important variation of (XM –Xm) and t during the 3rd phase.
The Moor Instrument software is able to determine, for each point of measurement, the value of flux F in arbitrary units, and of the time in seconds elapsed since the beginning of the investigation. It is able to select a portion of the laser doppler recording and to calculate minimal, maximal, median and mean values , standard deviation of flux F and the duration t (in seconds) of the selected portion.
Basis values of flux are not significant, because they depend on the position of the laser doppler probe ; we study the variation of microcirculation when tourniquet is deflated and just after.
For each investigation of F we measure minimal value Fm, obtained just before tourniquet is deflated, and maximal values FM. We calculate time t between minimal and maximal values.
For each recording we calculate (FM –Fm) / t.
This value represents the curve slope when tourniquet deflates.
The calculated values are ordered into 2 groups : healthy leg in the former control group and lymphedema in a latter group.
For each group we calculate mean value of DF = FM - Fm and the mean value and standard deviation of t and (FM –Fm) / t.
To avoid too many data , we give mean values and standard deviations of the 2 groups only (table 1, 2)

	$\overline{\Delta F}$
HEALTHY LEG	19,6
LYMPHEDEMA	8,22

table 1

	N	$\bar{t}$	SD	$\overline{\Delta F/t}$	SD
HEALTHY LEG	23	1,88	0,99	10,42	7,3
LYMPHEDEMA	23	13,48	7,14	0,61	0,22

table 2

Statistical study

This study include 2 parts; a global and an individual study.

Global study

Measurement results are divided into 2 different groups (one with lymphedema, the other with controlateral leg).
A global statistical study is carried out to show whether there is a difference of microcirculation between the 2 groups or not. We compare the mean values (table 2) of the 2 parameters: t, (FM – Fm)/t with a Student test.
For each studied parameter, the results of the test show a significant statistical difference ($p < 10 - 4$).

Individual study

For each patient, we compare the values of the 2 parameters : t, (FM –Fm) / t obtained during laser doppler recording on the leg with lymphedema to those obtained on the healthy controlateral leg.

	t	ΔF/t
U_{th}	2	2
U_{cal}	5,40	2,22

table 3

To do so, we use a matched variable test. We choose risk at a = 0,05, the calculates values of U are shown in table 3. It appears from the table, that there is a significant difference between parameters obtained on the leg with lymphedema and those on healthy controlateral leg.

IV DISCUSSION

The results of the 2 statistical investigations show a variation in microcirculation induced by lymphedema. Peripheral lymph drainage is influenced by micro-rheological parameters [1] : tissue pressure, lymphatic endothelium structure, respiratory moving, artery beats, lymph structure, self activity of lymphatic collectors. Using a venous tourniquet allows us to relate microcirculation variations to 2 factors : first the decrease of storage capacity (tissue pressure, lymphatic collectors activity) and flow hindrance (muscular activity, lymphatic collectors activity, lymph structure, lymphatic endothelium structure). At first, we study the storage capacity of blood in the leg. The blood quantity stored by the venous tourniquet could be assessed by the variation of F during tourniquet deflates. It is proportional to the differences DF = FM -Fm . Observing table 1, we note that mean values of DF of the healthy leg control group are much higher than those of lymphedema group. We conclude that the storage capacity has decreased because of lymphedema [3] [4].
The results could be compared with those obtained with venous plethysmography. For each patient the decrease of storage capacity is proportional to the volume of the lymphedema.
Now, we study the microcirculation flow. Comparing the mean values for the healthy group to those of the lymphedema group (table 1) or for each patient the t value of the healthy limb to that with lymphedema, we notice that t is significantly more important for affected limb. We conclude that there is an important flow hindrance inducing the decrease and slowing down of microcirculation. The results of this study are in accordance with others results 12] and appear in contradiction with others studies showing microcirculation increase on the leg with lymphedema [5] [6] [9]. The study of THEYS (and co) was carried out on old lymphedema, stade III, with fibrosis. The clinical situation of these patients was the same that our patients. In our study, lymphedema are advanced, undepressive, with fibrosis, not improve by physiotherapy treatment. .The 2 studies show a microcirculation decrease in the leg with lymphedema. The studies [5] [6] [9] are carried out on young depressive lymphedema, stade I or II, with

out fibrosis, reduce by physiotherapy treatment. Contrary to our study, microcirculation increases in pathologic limb.
We conclude, that during the evolution of lymphedema, the microcirculation increases at first and decreases with the appearance of fibrosis.
Microcirculation decrease could be considered as a pejorative factor inducing a bad forecast concerning the efficiency of physiotherapy treatment.

REFERENCES

1. CASTENHOLZ A. , RÜHLING H.
Rheologie des peripheren lymphe . Eur J Lymph 1995 . 5 : 129-33
2. CLUZAN R.
Remarques à propos des aspects anatomiques de l'insuffisance lymphatique. Lymphatique et souffrance tissulaire , éd Lab Boots-Dacoor , Courbevoie , 1981 ; 25-34
3. DURAND A. , THIBAUT G.
Lymphedema and microcirculation : study on 23 cases
The European Journal of Lymphology - Vol. VIII - Nr. 31 - 2000 - p 63
4. DURAND A. , THIBAUT G.
Microcirculation and lymphedema
19th World Congress of International Union of Angiology -5 mai 2000 GAND (Belgique)
5. FISCHER M. , COSTANZO U. , HOFFMANN U. , BOLLENGER A. , FRAZECK UK.
Flow velocity of cutaneous lymphatic capillaries in patients with primary lymphedema . Microcirculation 1997.17 : 143-9
6. FISCHER M. , FRANZECK UK. , HERRIG I. , COSTANZO U. , WEN S. , SCHESSER M. , HOFFMANN U. , BOLLINGER A.
Flow velocity of single lymphatic capillaries in human skin . Am J Physiol 1996 . 270 : H 358-63
7. FÖLDI M.
Disease of lymphatics and lymphcirculation . BUDAPEST , Akademia Kiado , 1969.
8. MASMAN AR. , CONOLLY WB.
Intermittent pressure in the management of post-traumatic oedema and lymphoedema .
Eng Med J. 2000 04 24 , 87-9 .
9. PARTSCH H. , RABE E. , STEMMER R. Traitement compressif des membres . Editions phlébographiques françaises Janvier 2000 : p 38-40 ;
10. ROMAIN D.
Artères , veines et système lymphatiques : des rapports étroits . Rapport de session du XIIIe congrès Int. Lymphologie . Revue de la veine et du lymphatique 1991 ; 7 : 22-5.
11. STOJANOVIC I. , THEYS S. , BUCHE M. , POMPILIO G. , LOUAGIE Y. , EUCHER P. , RISTIC M. , JAMART J. , SCHOEVAERDTS J.C.
Laser Doppler in Assessment of Microcirculatory . Effectsof Boflomedil in Treatement of Inoperate Stages of Peripheral Arterial Occlusive Disease ;
Cardiovascular Surgery Sep 1996 p 54
12. THEYS S. , RAILLART V. , JAMART J. , SCAVEE V. , SCHOEVAERDTS J.C.
Skin microcirculation modifications in upper limb lymphoedema
The European Journal of Lymphology - Vol. VIII - Nr. 31 – 2000 – p 63

THE EUROPEAN JOURNAL OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

LIMITS OF SELF MANAGEMENT OF LYMPHEDEMA

Anne-Marie Vaillant-Newman, PT,MA.
Director
Pacific Therapy Education, Inc.
amvnewman@aol.com
www.lymphedemamanagement.com

ABSTRACT

***Background and purpose**: Self-management is considered an important part of the patient's ability to control her/his lymphedema and carry on with the treatment techniques implemented by professionals. The purpose of this research study is to assess the ability of patients with lymphedema to perform self-treatment. Self-management of lymphedema included self-manual lymph drainage, lifestyle constraints, precautions to observe, and compression garment management.*

***Method**: A survey was administered one month and one year after the patient had been discharged from physical therapy. A total of 18 patients were enrolled in the study.*

***Results**: 87% of the patient population was still performing their self-treatment as instructed one month after discharge, only 38.88% one year after discharge. Self-manual lymph drainage was the part of self-treatment most frequently neglected. All the patients wore their compression garments; some individual adaptations were recorded.*

***Discussion and conclusion**: Self-manual lymph drainage was the part of self-treatment most frequently neglected. Self-manual lymph drainage requiring the intervention of a family member, as in the treatment of the lower extremity, was the most frequently abandoned for diverse reasons. Some patients had the opportunity of being treated twice during the year following their initial treatment, and were achieving better self-treatment as a result. It seems that comprehensive instruction is required prior to discharge and that periodic reviews are necessary.*

***Key Words:** Lymphedema management. Self-treatment.*

INTRODUCTION

Developing the self-management of lymphedema, a chronic condition, is a logical concept. It is a significant part of lymphedema management, the main goal of which is the reduction of lymphedema and the maintenance of this reduction. Intervention of the patient in maintenance develops and maintains awareness of her/his own condition. It is necessary to evaluate the ability of the patient to carry on self-treatment and to explain the limits of her/his intervention. Some aspects of self-management sometimes require the intervention of a family member or home health attendant whose training and skills evaluation are also necessary. The function of the physical therapist is to check the maintenance of every aspect of self-treatment as well as to implement appropriate programs to correct errors and insufficient interventions.

PURPOSE

The purpose of this study was to assess the ability of patients with lymphedema to perform their self-treatment. Self-management included: self manual lymph drainage, observation of life-style constraints and precautions, and compression garment management.

METHODS

Eighteen patients with lymphedema were randomly selected from the Walker Physical Therapy lymphedema patient population. Four of these patients were treated twice in the one-year period. Every patient received education in self-manual lymph drainage as well as education in precautions, life-style constraints, and compression garment management. About 1/5 of the treatment time was devoted to self-treatment education. Prior to discharge patients were provided with supportive documentation: list of precautions as well as pictures of the different sequences of self-manual treatment. Every patient was aware of the necessity to renew the compression garment every six months. See figures 1 and 2 for stages of self manual lymph drainage of the upper extremity and list of precautions for upper extremity lymphedema. Prior to discharge, every patient was tested on knowledge of precautions and life style constraints. Every patient had to demonstrate the ability to perform self-manual lymph drainage and donning and doffing of the compression garment. Family members or home health attendants were also tested on the specific function that they had to perform, mainly assistance in donning and doffing of the compression garment, and sometimes the practice of simplified form of manual lymph drainage on the lower extremity. A survey was administered to these randomly selected patients, one month and one year after discharge.The physical therapist questioned 8 out of 18 patients directly: the remaining 10 were questioned via telephone. The goal of the telephone conversation was clearly explained to the patient. Patients were asked to reply honestly in order to assist in the collection of data for a scientific study. Patients were informed of the anonymity of their replies. See Table 1 for demographics and survey results.

RESULTS

16 patients out of 18 (88.88%) were still performing their self-manual lymph drainage 1 month after discharge from the facility. The two patients who reported that the manual lymph drainage was not performed any more were suffering from Lower extremity lymphedema and had to be assisted with the manual technique. "I thought that my wife was not performing the technique like you do. I was not confident. I suggested that we discontinue the practice of manual technique." One year after discharge from the facil-

ity, 5 out of 6 patients with lower extremity lymphedema were not receiving manual lymph drainage any more. The feeling of inaccurate application of the maneuver by a family member was the reason cited by 3 of them: the 2 others blaimed the lack of time in their daily schedule. A total of 7 patients out of 18 (38.88%) were not performing or receiving self-manual lymph drainage any more one year after discharge. One patient with lymphedema of the upper extremity demonstrated a totally original technique of self-manual lymph drainage; consequence of personal adaptation. 6 out of 18 patients (33.33%) lost or did not consult their list of precautions after discharge from the facility. One patient posted her list of precautions on the front of her refrigerator for easy access. All the patients wore their compression garment daily. The only exception was this patient who decided to wear the garment with which she had been previously fitted instead of the most recent one. Only 7 patients out of 18 (38.88%) answered "yes" to four questions:

Do you still practice self manual lymph drainage:

1) One month after discharge?
2) One year after discharge?
3) Do you still consult your list of precautions?
4) Do you wear your compression garment daily?

DISCUSSION

Out of 18 patients who had received a thorough education in self-management of lymphedema only 7 or 38.88% were still performing the self manual lymph drainage, observing precautions and wearing their compression garment one year after discharge from physical therapy. This low percentage raises the notion of necessity of re-evaluation and performance of reinforcement or refreshment sessions in order to maintain the practice of self-management of lymphedema. This low percentage also highlights that every patient is not sufficiently disciplined to carry on with treatment techniques. Only 4 patients were referred to physical therapy twice in the time frame of one year. Their compression garment was renewed as recommended about six months after the initial fitting. This means that the other patients either did not have a chance to get a new compression garment after six months or managed to proceed independently. This second observation shows that there is a need for implementing a specific program and a follow-up for patients with lymphedema. These observations confirm that physical treatment of lymphedema must be included in a program with periodic follow-up sessions. This would allow the physical therapist to review the sequences of self-management with the patient and to fit the patient with a new compression garment when needed. If self-management of lymphedema is not included in a program with periodic follow-up, it will not be carried over by the patient.

CONCLUSION

Self-management of lymphedema proved to be effective in this study in only 38.88% of the cases after one year. Self-manual lymph drainage is the most challenging part of self-treatment. Self-management is a necessary part of physical treatment of lymphedema however it requires periodic sessions of reinforcement. Follow up sessions are necessary to re-evaluate the patient, update patient's knowledge in self-treatment and fit the patient with a new compression garment when needed.

Repeated studies would determine is higher level of intervention is effective.

Patients	Age	Site of LE	Practice of	Self-MLD	List of	Precautions	Compression	Garment
			30 days post-D/C	1 year post-DC	Still available	Lost or not consulted	Worn daily	Not Worn
1	70	U.E.	Yes	Yes	Yes		Yes	
2	39	U.E.	Yes	Yes		Not consult.	Yes	
3	48	L.E.	No	No	Yes		Yes	
4	42	L.E.	Yes	No		Not consult.	Yes	
5	72	U.E.	Yes	Yes	Yes		Yes	
6	68	U.E.	Yes	Yes	Yes		Yes	
7	79	U.E.	Yes	Yes***	Yes		Yes	
8	65	U.E.	Yes	No		Lost	Yes	
9	47	U.E.	Yes	Yes	Yes		Yes	
10	67	U.E.	Yes	No	Yes		Yes	
11	78	U.E.	Yes	Yes	Yes		*	
12	66	U.E.	Yes	Yes	Yes		Yes	
13	69	L.E.	No	No		Lost	Yes	
14	82	U.E.	Yes	Yes	Yes**		Yes	
15	35	U.E.	Yes	Yes		Not consult.	Yes	
16	81	L.E.	Yes	No	Yes		Yes	
17	76	L.E.	Yes	No		Not consult.	No	
18	81	L.E.	Yes	Yes	Yes		Yes	

LEGEND: * Patient wore her used compression garment instead of the new one. ** Patient placed her list of precautions on the front of her refrigerator. *** Patient had modified the technique of self-MLD. **LE:** Lymphedema. **MLD**: Manual lymph drainage. **Post-D/C:** After discharge from the facility. **U.E.:** Upper Extremity. **L.E.:** Lower Extremity.

Patients	Age	Site of LE	Practice of Self-MLD		List of precautions		Compression garment	
			30 days	1 year	30 Days	1 year	30 days	1 year
			post-DC	post-D/C	post D/C	post D/C	post-D/C	post D/C
							Worn?	Worn?
1	70	U.E.	Yes	Yes	C.	C.	Yes	Yes
2	39	U.E.	Yes	Yes	N.C.	N.C.	Yes	Yes
3	48	L.E.	No	No	C.	C.	Yes	Yes
4	42	L.E.	Yes	No	C.	N.C.	Yes	Yes
5	72	U.E.	Yes	Yes	C.	C.	Yes	Yes
6	68	U.E.	Yes	Yes	C.	C.	Yes	Yes
7	79	U.E.	Yes	***	C.	C.	Yes	Yes
8	65	U.E.	Yes	No	C.	Lost	Yes	Yes
9	47	U.E.	Yes	Yes	C.	C.	Yes	Yes
10	67	U.E.	Yes	No	C.	C.	Yes	Yes
11	78	U.E.	Yes	Yes	C.	C.	Yes	Yes
12	66	U.E.	Yes	Yes	C.	C.	Yes	*
13	69	L.E.	No	No	C.	Lost	Yes	Yes
14	82	U.E.	Yes	Yes	C. **	C.	Yes	Yes
15	35	U.E.	Yes	Yes	N.C.	N.C.	Yes	Yes
16	81	L.E.	Yes	No	C.	C.	Yes	Yes
17	76	L.E.	Yes	No	N.C.	N.C.	Yes	Yes
18	81	L.E.	Yes	Yes	C.	C.	Yes	Yes

LEGEND: * Patient wore her used compression garment instead of the new one. ** Patient placed her list of precautions on the front of her refrigerator. *** Patient had modified the technique of self-MLD. **LE:** Lymphedema. **MLD:** Manual Lymph Drainage. **Post D/C:** After discharge from physical therapy. **U.E.:** Upper Extremity **L.E.:** Lower Extremity. **C:** Consulted. **N.C.:** Not Consulted.

REFERENCES:

The Diagnosis and Treatment of Peripheral Lymphedema. Consensus Document of the International Society of Lymphology Executive Committee. Lymphology 28 (1995) 113-117

Runowicz C.et al. Patient Education-Pre and Post Treatment. American Cancer Society Lymphedema Workshop. Cancer: Interdisciplinary International Journal of the American Cancer Society, Volume 83, 1998, 2880-2881

Runowicz C. Lymphedema: Patient and Provider Education. Current status and Future Trends. American Cancer Society Workshop. Cancer: Interdisciplinary International Journal of the American Cancer Society, Volume 83, 1998, 2874-2876

Kirshbaum M. The development, Implementation and evaluation of guidelines for the Management of Breast Cancer Related Lymphoedema. Eur J Cancer Care 1996;5:246-51

Rockson S. Precipitating Factors in Lymphedema: Myths and Realities. American Cancer Society Workshop. Cancer: Interdisciplinary International Journal of the American Cancer Society, Volume 83, 1998, 2814-2816

Andrade MFC. et al Patient's Education as a cornerstone of Good Results in a Lymphedema Center. Progress in Lymphology XVI Lymphology 31 (Suppl) (1998) 434-436

THE EUROPEAN JOURNAL
OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

EFFICACY AND TOLERABILITY OF PROTEOLYTIC ENZYMES AS AN ANTI-INFLAMMATORY AGENT IN LYMPHOEDEMA AFTER AXILLARY DISSECTION DUE TO MAMMARY CANCER

Kasseroller, R.[1], *Wenning, H. G.*[2]

1 Privatklinik St.Barbara, Gefäßzentrum, Rödhammer Weg 9,1 5424 Bad Vigaun, Austria
2 MUCOS Pharma GmbH & Co., Malvenweg 2, 82538 Geretsried, Germany

ABSTRACT

Aim of the study was to investigate the influence of a proteolytic enzyme, the drug Wobenzym, (Mucos Emulsionsges. mbH, Wien, Austria), on the volume of the lymphoedema in the limb and the fibrotic changes in the tissue in secondary lymphoedema patients after axillary lymph node dissection due to mammary cancer who received combined decongestive physical treatment (CDT).

METHODS:

Randomised, placebo controlled, double blinded study, carried out over one year in a lymphoedema treatment centre. 88 patients have been included and analysed according to the blind review report using a univariate one sided Wilcoxon Mann Whitney test for difference for the primary criterion volume reduction (confirmatory analysis).
The secondary variables CRP value in the blood, skinfold thickness, tension, and global judgement of efficacy by both the investigator and patient underwent exploratory interpretations. The visits for measurements were scheduled on the days 1, 9, 19 and 45, except for CRP measurement which was performed on days 1 and 19 only. The CDT was applied from day 1 through day 20.

RESULTS:

Volume: Starting with baseline measurements of the ill arm of a mean of 2483.0 (verum) and 2420.1 (placebo) both groups show a decrease of volume until day 45 with final means of 2275,1 (verum) and 2225,7 (placebo).
CRP: In patients with positive CRP- values at baseline there has been a mean percent change from baseline of minus 39.8% as compared to visit 3, while in the placebo group there has been a percent change of minus 17.4% .
Skinfold Thickness: A parameter for the fibrosis. Starting with a baseline thickness in the lower arm of 3.7 mm (verum) and 5.0 mm (placebo) both groups show decrease of the thickness until day 45 with final means of 3.0 mm (verum) and 4.0 mm (placebo). The mean percent change at the final visit 4 from visit 3 was shown with – 0.19% for the verum group. The placebo group showed a marginal mean increase at the visit 4 from visit 3 with + 2.2%. Starting with a baseline thickness of the skin of the hand of 6.5 mm (verum) and 4.3 mm (placebo) both groups show decrease of the thickness until day 45 with final means of 3.8 mm (verum) and 3.0 mm (placebo). The verum group is showing a better development with regard to the means between visit 2 and visit 4. In the upper arm and the fingers no group difference in decreasing the skinfold thickness was shown.
Tension: It was assessed by the investigator by means of a 4-point scale. Starting with a baseline mean tension of 2.0 (verum) and 1.8 (placebo) both groups show a decrease of tension until visit 4 with final means of 0.4 (verum) and 0.5 (placebo).

CONCLUSION

For the primary criterion Volometer® measurements the study failed to demonstrate efficacy of the test preparation Wobenzym®. The difference in volume reduction between the two groups is negligible.
Nevertheless, fibrotic changes have far better been reduced in the verum group, not from the very beginning of the treatment , but in the second half of treatment, meaning that the result of the CDT maintains better. The inflammation related parameters (tension, CRP) have a better outcome in the verum group compared to the placebo.
The CDT is the golden standard in lymphoedema treatment, an improvement by anti-inflammatory therapy with proteolytic enzymes seems to be possible.

KEY WORDS:
Lymphoedema, oedema volume, fibrosis, skinfold thickness, cellulites, combined physical decongestive treatment, manual lymphatic drainage, compression, enzymes, anti-inflammatory therapy, tension, CRP

INTRODUCTION

Lymphoedema is a chronic and sometimes very progressive disease caused by the damage of lymphatic vessels due to surgical treatment and or radiotherapy (secondary lymphoedema) Another cause is the malformation or lack of lymphatic vessels (primary). The current treatment option for this entity is the combined physical decongestive therapy (CDT)(1, 2, 11).
Former results of medication were not satisfying or having to much negative side effects like.

AIMS

The aim of this study was to demonstrate the efficacy and tolerability of the proteolytic enzyme combination preparation Wobenzym, (Mucos Emulsionsges. mbH, Wien, Austria), containing Pankreatin 100mgs, Papain 60 mgs, Bromelain 45 mgs, Trypsin 24 mgs, Lipase 10 mgs, Amylase 10 mgs, a-Chymotrypsin 1mg, Rutoside 50 mgs assignable in additional reduction of arm volume (primary criterion) in patients with secondary arm lymphoedema after dissection of axillary nodes due to

mammary cancer. Secondary criteria were improvement of the skinfold thickness as a parameter for the fibrotic changes in the tissue, CRP values, tension, and global judgement of the efficacy by both investigator and patient. Previous studies have demonstrated a benefit through an approximate mean reduction of the oedema volume of about 40%, which is lost very soon after ending this treatment. By applying a concomitant proteolytic enzyme therapy the patients condition should have been improved so that this intensive CDT treatment showed longer lasting benefit. Therefore a follow up period of four weeks was implemented to investigate the efficacy parameters.
Secondary variables were examined because of the chronic inflammatory conditions in lymphoedema (1, 2, 3).
Lymphoedema tissue with its high protein oedema fluid is predetermined for erysipelas and cellulites induced by streptococcus infection. Options supporting the patients benefits with anti-inflammatory medications (5) has therefore been discussed.
Repeated studies would determine is higher level of intervention is effective.

METHODS

Study Design and Statistical Methods
The randomised, placebo controlled double blinded, two tailed, mono centric case control study was performed over one year. It was enrolled in June 1999 and finished in August 2000.
The performance of the study was in accordance with the ICH and GCP-guidelines. Data were managed and analysed using statistical software programs of IDV-Data Analysis and Study Planning, Gauting/Munich (REPORT, TESTIMATE, SmarTest, RANCODE, Nnpar).
All patients received the golden standard treatment, the combined decongestive therapy (CDT), comprising the manual lymphatic drainage on affected sites, started with lymphatic drainage on the neck, arm and thorax, with consecutive bandaging of the affected arm and specially designed exercises and skin care. The CDT was applied twice daily, each session for 60 minutes, from day 1 to day 20.From day 20 to day 45 the bandages were replaced by a costume made flat knitted garment, compression class II.
Thus the final visit was calculated for day 45.
The selection of the doses was based on the results of clinical studies in patients with lymphatic oedema after axillary dissection due to mammary cancer (7, 8, 9). This resulted in a dose of 5 enteric coated tablets three times daily over 6.5 weeks for each patient .
As predefined in the study protocol the univariate directional Wilcoxon Mann Whitney Test for the primary criterion volume change, measured by means of a Volometer® at the end of the study (visit 4, day 45) should have been performed two-sided. The multiple level alpha of the study with potentially two stages was o.o5.
A Blind Review was carried out following the framework of the requirements of the ICH Guideline E9 (ICH Topic E9, Statistical Principles for Clinical Trials, Step 4, Consensus guideline, 5th February 1998, CPMP/ICH/363/96).
Due to the Blind Review Report the confirmatory analysis is based upon the primary criterion: Volometer®, operationalised as Volometer® measurement an the ill arm at visit 4, percent change from baseline, last value carried forward (LVCF), intent to treat (ITT) data set (full analysis set). The analysis was performed by means of the Wilcoxon-Mann-Whitney test as a one-sided test for difference. As defined in the study protocol the study was conducted as a two-stage-procedure (Bauer and Köhne, 1994): with a p-value above 0.5 the study had to be terminated due to lack of efficiency, with a p-value below 0.0102 the study had to be terminated with a positive (statistically significant) result, and with p-values between 0.0102 and 0.5 the second stage of the study had to be planned and carried out according to the guidelines of Bauer and Köhne (adaptive design).
If superiority of the test drug is statistically proven for visit 4 the same test can be applied to visit 3 (day 19) with full alpha (according to the principle of a priori ordered hypotheses (Maurer, Hothorn, Lehmacher, 1995).
All results will be presented as Mann-Whitney estimators (measure of relevance) and their one-sided 98.98% confidence interval (CI, according to alpha = 0.0102 for the first stage of this study)
Stratified analyses of volume, tension, CRP values and skinfold thickness with regard to anamnestic radiation, hormone therapy, chemotherapy, incidence of erysipelas were additionally carried out in the sense of descriptive data analyses.
Data validation and analyses for responsiveness have been performed by means of basic statistics, pre-post scattergrams, correlation analyses and histograms. Change from baseline values and percent change from baseline values have been calculated and analysed.
The pattern of missing values has been analysed for the efficacy criteria. Missing values have been primarily observed at the end of the study. Thus the introduction of the Last-Value-Carried-Forward technique (LCVF) was justified.

Study Population
The study population comprises of patients with one sided secondary arm lymphoedema after dissection of the axillary lymph nodes (level I or II according to the St. Gallen consensus conference) due to mammary cancer, who have been treated with CDT at the Wittlinger Therapy Centre in Austria. 88 female patients aged between 30 and 80 were selected by the investigator considering the predefined inclusion and exclusion criteria. A patient number was allocated to the patients in uprising arithmetical order and the corresponding medication was handed out. The medication itself was randomly allocated to either of the two treatment groups (RANCODE, block size: 4). Neither the investigator nor the patient knew which preparation was administered.

Inclusion criteria were:
- patients with one-sided lymphatic oedema after axillary dissection due to mammary cancer, stage II to II
- age ≥ 30 years and < 80 years
- written, signed informed consent obtained.

Exclusion criteria were:
- known pregnancy or lactation
- history of intolerability to enzyme preparations or to the passive ingredients
- arterial closures and/or flow-off disorders at the ill arm and/or contra lateral arm
- connate lymphatic oedema
- treatment with venoactive drugs such as Rutosides,

Bioflavonoides, Aescin, etc.
- treatment with NSAIDs
- contraindication for lymphatic drainage
- participation in any clinical study in the last 30 days
- simultaneous participation in any other clinical trial

A total of 88 recruited patients (100%) have been included in the intent-to-treat (ITT) analysis. 17 patients had to be excluded from the per-protocol analysis 1 (PP1, visit 4) due to major protocol violations, and likewise 5 patients had to be excluded from the PP2 analysis (visit 3). The following figure gives a survey on the disposition of patients (Figure 1).

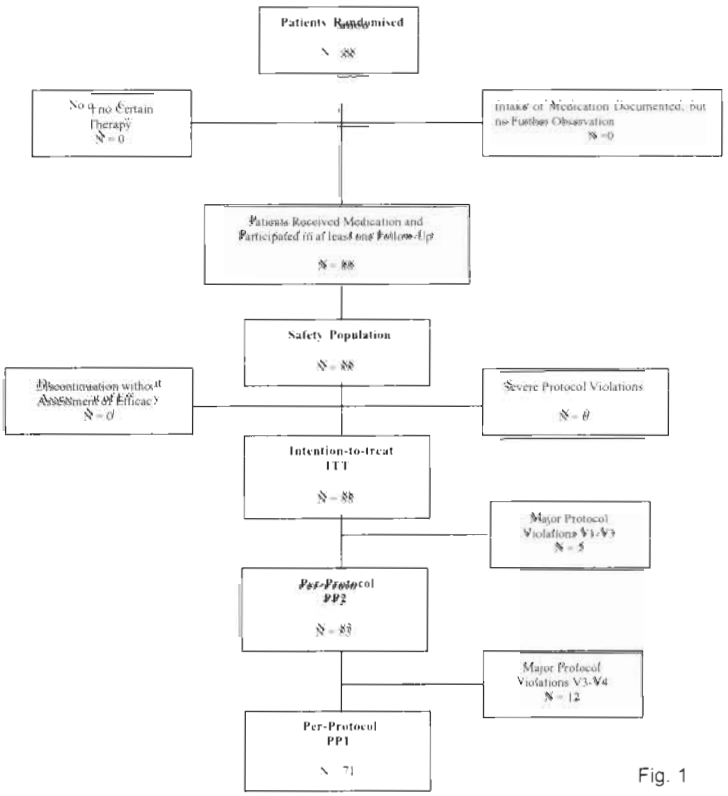


Fig. 1

Study Instruments and Examination Protocol

For measuring the indicator volume reduction in arm lymphoedema a Volometer, (Bösl, Aachen, Germany) was used. This opto-electronic device measures the arm circumference 2-dimensionally along a distance of 45 cm on the entire arm and then calculates the volume of the arm according to the Kuhnke formula (4). 225 infrared diodes and corresponding sensor cells in two dimensions and a microprocessor steering are used to achieve a high accuracy (0.5%). As reference the healthy arm of each individual is measured. The indicators skinfold thickness defined also as skinfold-ratio was measured with a calliper in mms and divided by 2 for the normal measurement of the skinfold in not fibrotically changed skin. Measures of the absolute values were taken from the upper arm, the lower arm, the hand, and from finger III. The absolute reference value is 2 mms for the healthy skin (6).

For the indicator tension, assessed by the investigator, a four point rating scale was used with no tension = 0, slight tension = 1, moderate tension = 2, and severe tension = 3. All these measurements were carried out on days 1, 9, 19 and 45. The CRP value was measured on days 1 and 19.

The normal negative level of CRP in capillary blood is below 10 mgs/l. CRP has been measured as laboratory parameter by means of a Nycomed, rapid test, delivering truncated data. CRP levels between 10mg/l and 300 mg/l are measured as numeric values. The following flow chart shows the schedule for assessment of efficacy and safety variables.

	Baseline Examination	Study visit	Study visit	Final Examination
Visit No.	1	2	3	4
Day of study	1	9	19	45
Inclusion, Exclusion criteria	×			
Demographic data	×			
Anamnesis	×			
Concomitant diseases	×			
Concomitant medication	×			
Change of concomitant diseases resp. conc. med.		×	×	×
Volometer® measurements	×	×	×	×
Tension	×	×	×	×
Skinfold thickness	×	×	×	×
CRP	×		×	
Adverse events		×	×	×
Dispense of study medication	×		×	
Compliance			×	×
Global judgment				×
Study exit				×

Fig. 2

In order to assess the patients suitability for the study the baseline exam was to be performed.

After the patient had consented their participation in the study the inclusion and exclusion criteria had to be verified.

The patient number was allocated to the patient in uprising arithmetical order and the patient received the first box of matching medication (300 tablets). The physical decongestive treatment (CDT) was applied in accordance with the study protocol.

The date of axillary dissection, the number and the time of erysipelas, radiation, chemotherapy, hormone therapy, concomitant diseases and medication had to be assessed.

After 9 days the first follow up was performed. The patient was to be inquired about adverse events. Changes in concomitant diseases or medication were to be documented.

After 19 days (end of hospitalisation) the second follow up was performed according the study protocol.

The patients received the second matching box of medication (400 tablets), the returned medication underwent a pillcount to check the consumption.

A final exam was performed 45 days after inclusion into the study or after premature study discontinuation.

This follow up exam was carried out at the investigators private practice in Salzburg, Austria.

Each patient was questioned about the target criteria according to the case report protocol.

The patient was inquired about adverse events, as well as about changes in concomitant diseases and medications.

The returned medication again underwent a pillcount and the consumption was documented.

The global assessment of both the physician and the patient with regard to efficacy and tolerability were to be documented.

The benchmark for compliance was set to a regular intake of not less than 80% and not more than 125 % of the test drug.

The per protocol population (PP) is divided in two data sets, the

PP1 for analysis of the results after visit 4 and the PP2 for analysis of the results after visit 3.
Patients with discontinuation before visit 4 are excluded from PP1, if discontinuation was not efficacy related.
They were excluded from PP1 and PP2, if the discontinuation was before visit 3. As already pointed out above the PP1 includes 71 of the 88 randomised patients and the PP2 includes 83 patients.

RESULTS

1. Demographic data and baseline characteristics

Both treatment groups were well comparable (mean verum/placebo, ITT data set, valid N: 44 each) regarding age (60.9/58.0), weight (78.31/76.77), and height (163.3/165.3).
The median time between the lymph node dissection and the baseline visit was 47.5 month in the Wobenzym® group and 48.0 month in the placebo group.
Only in the frequency counting of radiation (yes/no) separately for the two treatment groups there were significantly more patients in the Wobenzym® group that had not undergone radiation in the past (15 verum/6 placebo, ITT data set, p = 0.0294).
Likewise in the frequency counting for hormone therapy (yes/no) there were significantly more patients in the placebo group that had not undergone hormone therapy in the past (17 verum/28 placebo, ITT data set, p = 0.0154).

2. Efficacy criteria

As primary criteria for efficacy the final percent changes of the Volometer® measurements on the ill arm had been defined.
All other criteria were only secondary criteria and have therefore only been interpreted exploratorily according to the ICH E9 guidelines.
Regarding the baseline efficacy criteria (ITT data set) again both groups are well comparable with the exception of the skinfold thickness of the hand (6.5 mm verum/ 4.3 mm placebo, p = 0.0078).

Volume

On the healthy arm in both groups the Volometer® measurements showed only negligible changes from baseline until the end of the study.
Mean values for visit 1 are: 1852.1 in the verum and 1843.1 in the placebo group, the final means at the end of the study (visit 4) were: 1816.9 (verum) and 1816.0 (placebo).
Thus, both groups show almost perfect stability of the volume of the healthy arm.
The groups are very well comparable during the whole course of the study.
On the ill arm starting with baseline Volometer® measurements of 2483.0 (verum) and 2420.1 (placebo) both groups show a decrease of volume until visit 4 (day 45) with final means of 2275.1 (verum) and 2225.7 (placebo).
Both groups show an almost identical course of the volumetric development between baseline visit and final end point visit.
It is interesting but well known to note that the main changes may be observed within the first week of the study (10).
The following figure shows the time course of the absolute values (means and standard deviation).

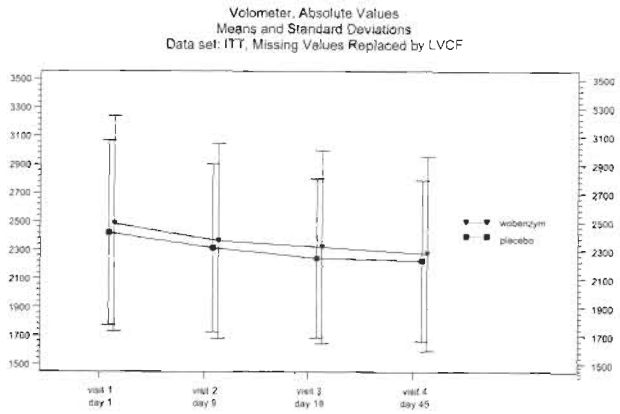


Fig. 3 - Volometer®, means and standard deviations (SD), ill arm

Both groups show an almost identical course of the Volometer® development between baseline visit and final visit with regard to the absolute values of the ill arm. Since lymphatic drainage was applied intensively as concomitant physical therapy for all patients between visits 1 (day 1) and 3 (day 19) a special supportive analysis has been carried out for the percent changes between visits 3 (end of lymphatic drainage) and 4 (end of observation period). Looking for the further development between visit 3 and 4 (i. e. after finishing the physical decongestive treatment) the following percent changes could be recorded (Figure 4):

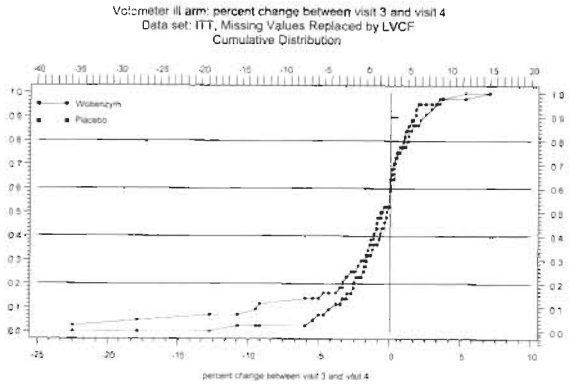


Figure 4: Volometer® percent changes between visit 3 and visit 4, ill arm:

It may be depicted from the figure above that there is a slight superiority of Wobenzym, for the development between visit 3 and visit 4 with regard to the percent changes of –5% and more (left part of the figure) with vertical distances of the two curves up to 10 percent of the patients (difference in proportion = 0.1), without statistical significance With regard to the smaller percent changes there is equality between medication and placebo. Thus some patients have advantages by this medication treatment between visit 3 and visit 4 regarding to the volume of the ill arm.

Skinfold thickness

On the upper ill arm starting with a baseline thickness of 7.4 mm in the verum group and of 6.7 mm in the placebo group at visit 4 a decrease was shown down to 4 mm in the verum and down to

3.4 mm in the placebo group.. For both groups the greatest decrease was shown between visits 2 and 3.
The picture (Figure 5) shows the time course of the absolute values (means and standard deviations):

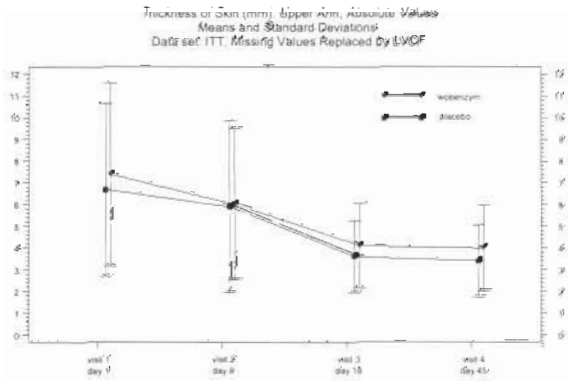


Fig. 5 - Thickness of the skin on upper arm, ill arm

Both groups show a very similar development of the skinfold thickness between baseline visit and final visit with regard to the results of the ill arm.
The % change from baseline at visits 2, 3, and 4 shows an over all identical scene .
Almost similar results were recorded for the measurements on the lower arm and the 3rd. finger for both the absolute values and the % change from baseline at visits 2, 3, and 4.
The above outlined results differ slightly from the results collected from the skinfold thickness of the hand.
The absolute values of the ill hand are shown in figure 6. Starting with a baseline thickness of 6.5 mm (verum) and of 4.3 mm (placebo) both groups show decrease of the thickness until visit 4 with final means of 3.8 mm (verum) and of 3.0 mm (placebo).

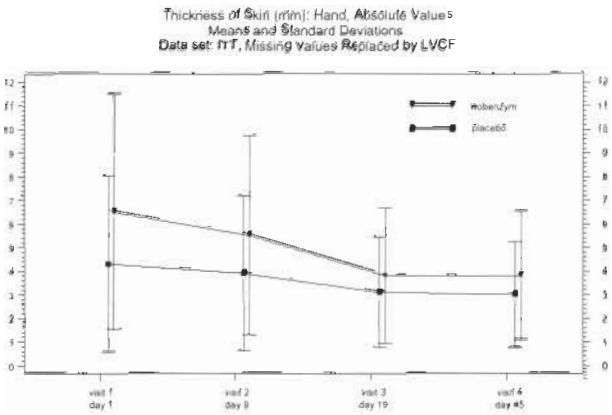


Fig. 6 - Thickness of the skin on hand, ill arm

The figure shows that there are some baseline differences with regard to the mean skinfold thickness of the hand.
Nevertheless, the verum group showed a better development with regard to the means. In the change from baseline for visits 2, 3, and 4 the verum group showed a final mean decrease of –2.8 mm (median –1.5 mm) whereas the corresponding value for the placebo group was –1.2 mm (median – 0.0 mm).
The results of the percent changes from baseline with regard to visit 2, 3 and 4 showed a mean reduction by –29.84% for the verum group and by –15,73 % for the placebo group.
Due to the skewed distribution of the percent changes the medians should rather be interpreted than the means: the corresponding figures are –33.0 % for the verum and – 0.0 % for the placebo group! Figure 7 outlines the % change from baseline at visit 4:

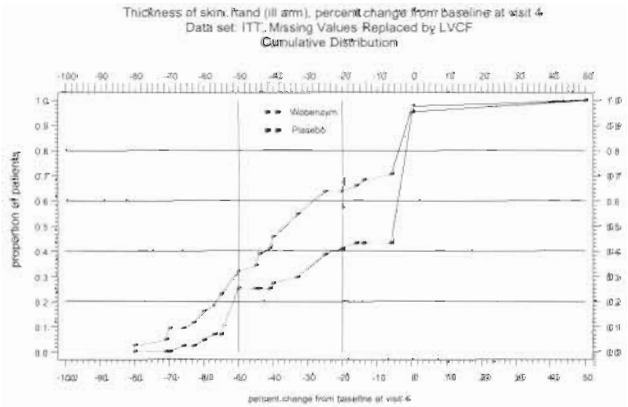


Fig. 7 - Thickness of the skin on hand, percent change from baseline at visit 4, ill arm

The picture of the cumulative curves for the hand is just the opposite of the situation of the lower arm.
For the hand superiority of Wobenzym® is shown throughout the most part of the scale.
A percent change of at least -50% is reached by 31.82% of the patients in the Wobenzym® group and by 25.0% of the patients in the placebo group.
A percent change of at least –20% is reached by 63.64% of the patients in the Wobenzym® group and by 40.91% of the patients in the placebo group.
The development between visit 3 and visit 4 showed only slight superiority for the verum group (mean decrease by – 2.84% whereas a mean increase by + 2.84% in the placebo group).
A further decrease was seen in 13.6% of the patients in the verum group and in 9.1% of the patients in the placebo group.

Tension

Figure 8 shows the absolute values of tension in the ill arm.

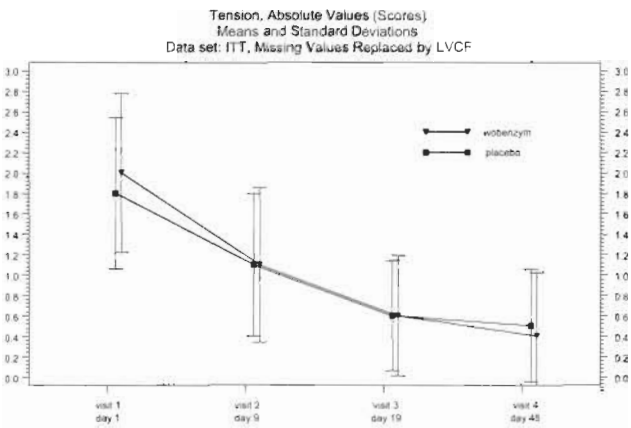


Fig. 8 - Tension ill arm

Starting with a baseline mean tension of 2.0 (verum) and 1.8 (placebo) both groups show an almost similar decrease of tension in the ill arm until visit 4 with final means of 0.4 (verum) and 0.5 (placebo).
The % change from baseline at visit 4 demonstrated by means of the cumulative distribution function shows superiority for the Wobenzym® treated patients especially at high reductions of tension (Figure 9).

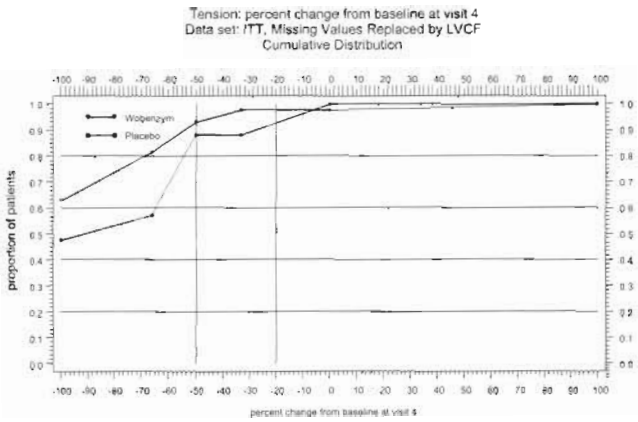


Fig. 9 - Tension, percent change from baseline at visit 4, ill arm

A percent change of 100% (total improvement) is reached by 62.79% of the patients in the Wobenzym® group and by 47.62% of the patients in the placebo group.
A percent change of at least – 50% is reached by 93.02% of the patients in the Wobenzym® group and by 88.10% of the patients in the placebo group.
And finally the percent changes between visits 3 and 4 – this was the time where no concomitant CDT was applied – shows a clear superiority of the Wobenzym® treated patients (Figure 10).

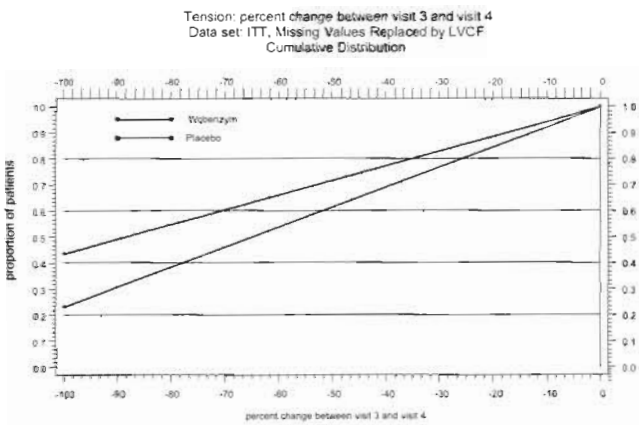


Fig. 10 - Tension, percent change between visits 3 and 4, ill arm

As may be depicted from the above figure there is clear superiority of Wobenzym® for the development between visit 3 and visit 4.
There are only patients with either 100% recovery from already existing tension at visit 3 (Wobenzym®: 43.5% of the patients, placebo: 23.1%) or with unchanged tension (Wobenzym®: 56.5% of the patients, placebo: 76.9%).
Thus, with regard to the tension between visits 3 and 4 a marked proportion of patients had advantage by Wobenzym® treatment.

CRP

CRP has been measured by means of a Nycomed® rapid test at visit 1 (baseline) and visit 3 (day 19).
The test delivers truncated data: CRP-levels below 10 mg/l (normal values) and CRP-levels above 300 mg/l cannot be differentiated by numeric values.
CRP-levels between 10 mg/l and 300 mg/l are measured as numeric values.
In a first step the CRP results have been dichotomised as (0) negative (for low = < 10 mg/l) and (1) positive (for high = >10 mg/l). There was no CRP level above 300 mg/l.
The following table (Table 1) shows the results of CRP as so-called "shift tables" showing directly the development between baseline and visit 3 within the groups.

Table 1: CRP, shift tables baseline vs. visit 3, ITT

Wobenzym®

CRPTick3 / CRPTick1	low	high	Total
low	27 64.3%	0 0.0%	27 64.3%
high	5 11.9%	10 23.8%	15 35.7%
Total	32 76.2%	10 23.8%	42 100.0%

Placebo

CRPTick3 / CRPTick1	low	high	Total
low	31 70.5%	0 0.0%	31 70.5%
high	1 2.3%	12 27.3%	13 29.5%
Total	32 72.7%	12 27.3%	44 100.0%

As may be depicted from the above table the Wobenzym® group is showing better results than the placebo group with regard to the CRP development between baseline visit and visit 3: out of 15 patients with positive (high) baseline findings five patients normalized (negative resp. low values) in the Wobenzym® group. Out of 13 patients with positive (high) baseline findings in the placebo group, only one patient normalized.
Analysis of marginal homogeneity indicates differences between baseline (visit 1) and final scores (visit 4) with regard to CRP for the Wobenzym® group (MW = 0.5595, P = 0.0086, test for marginal homogeneity, exploratory interpretation) but not for the placebo group (MW = 0.5114, P = 0.1559, test for marginal homogeneity, exploratory interpretation).
I a second step absolute values between 10 mg/l and 300 mg/l have been used by treating the results as follows (CRP was assessed using absolute values):
- Truncated result CRP< 10 mg/l: substitution by an absolute value of 0 mg/l.
- Results between 10 mg/l and 300 mg/l: use of absolute measurement.
- (there have been no CRP values > 300 mg/l).
The following table shows the results of the absolute values of the CRP measurement for the
patients with positive CRP-values at baseline with classical and robust statistics for the ITT data set, separately for the two groups. The abbreviations are as follows:

- CRP-absol1: absolute values visit1
- CRP-absol3:absolute values visit3
- CRP-%: percent changes of absolute values

Table 2: CRP, absolute values, patients with positive baseline CRP, ITT

		CRPabsol1	CRPabsol3	CRP-%
Wobe-ITT	Mean	36.5	23.3	-39.764
	Std Dev	22.79	24.29	44.9198
	Min	10	0	-100.00
	Lo Quar	22.0	0.0	-100.000
	Median	30.0	22.0	-10.000
	Up Quar	49.0	34.0	-3.922
	Max	100	90	0.00
	Valid N	15	15	15
Place-ITT	Mean	32.1	26.1	-17.356
	Std Dev	16.65	17.61	26.4397
	Min	12	0	-100.00
	Lo Quar	23.0	14.0	-16.667
	Median	25.0	24.0	-8.333
	Up Quar	42.0	29.0	-4.167
	Max	61	60	0.00
	Valid N	13	13	13

As may be depicted from the table above for patients with positive CRP-values at baseline there has been mean percent change from baseline of –39.8%, while in the placebo group there has been a mean percent change of -17,4%.
The following figure (Figure 11) shows the results for the comparison of the Wobenzym® group and the placebo group for the percent changes of the CRP-values between visit 1 and visit 3 (ITT data set, patients with positive CRP at baseline) as cumulative distribution function.
Thus the group differences are presented for the whole distribution.

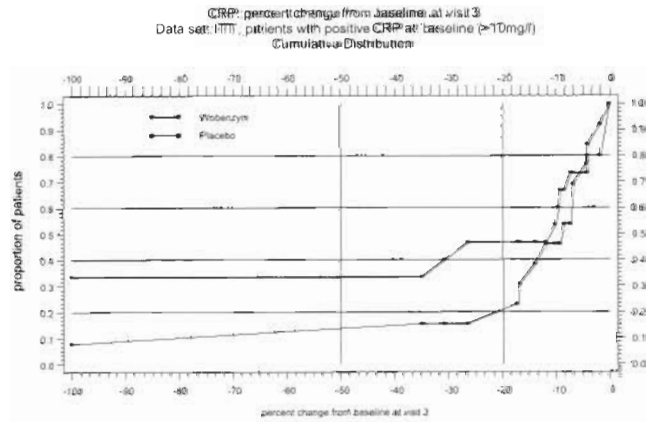


Fig. 11

The figure depicts a clear superiority for the verum group for the CRP development between visit 1 and visit 3.
Thus a marked proportion of patients with positive baseline CRP had advantage by the enzyme treatment.
A percent change of at least 50% was reached by 33% of the patients in the verum group and by 7,7% of the patients in the placebo group.
A percent change of at least –20% was reached by 46,7% of the patients in the verum group and by 15,4% of the patients in the placebo group. Nevertheless, the small number of patients (n = 15 versus n = 13) has to be respected when interpreting the results.

Further supportive analyses

Stratified analyses with regard to the anamnestic criteria erysipelas, radiatio, chemotherapy, and hormone therapy have been performed for the final percent changes of the tension in order to check the prognostic relevant factors of this responsive efficacy criterion.
For chemotherapy relevant differences have been found regarding both subgroups (with/without chemotherapy).
The following table (Table 3) shows the result of the stratified analysis for chemotherapy.

Table 3: tension, final percent changes, Wobenzym® vs. placebo, stratified analysis for chemotherapy, ITT

Cochran-Mantel-Haenszel Pooling
Peto-Wilcoxon Test - Criterion: Tension 4%

STRATA	STATISTICS	GROUPS Wobe-ITT	Place-ITT
no	N	28	22
	Valid	27	21
	Censored	-	-
	Events	27	21
	P =0.0283	(Chi_= 4.8085, DF= 1)	

STRATA	STATISTICS	GROUPS Wobe-ITT	Place-ITT
yes	N	16	22
	Valid	16	21
	Censored	-	-
	Events	16	21
	P =0.9345	(Chi_= 0.0067, DF= 1)	

STRATA	STATISTICS	GROUPS Wobe-ITT	Place-ITT
Combined	N	44	44
	Valid	43	42
	Censored	-	-
	Events	43	42
	P =0.0975	(Chi_= 2.7456, DF= 1)	

Proportional Hazard/Odds Ratio and Confidence Interval
(Variance Estimate: Cox-Mantel)
Reference group: Place-ITT

Strata	Statistic	99.0% CI (LB, UB)
no	3.7994	(1.1105, 12.9993)
yes	0.9481	(0.2911, 3.0877)
Combined	1.8448	(0.7871, 4.3240)

The table above shows relevant differences between the results within the two subgroups (patients without chemotherapy: odds ratio 3.799 P = 0.0283; patients with chemotherapy: odds ratio 0.9481, P = 0.9345).
The combined odds ratio with adjustment for strata (1.8448) shows more than small superiority of the enzyme preparation (benchmark for small superiority 1.438).
For the subgroup no chemotherapy the odds ratio (3.7994) shows medium to large superiority.
Thus the chemotherapy has prognostic value for the outcome of the tension

Safety

Out of 88 patients no one (0.0%) was excluded from the safety population. No serious adverse events occurred during the course of the study.
Over all, 15 adverse events (AEs) were recorded, 7 (15.9%) for the verum group and 8 (18.2%) for the placebo group likewise.
The 7 AEs in the verum group were all gastrointestinal complaints of moderate intensity and rated as possibly (6 cases) or definitely (1 case) related to the study medication. 5 (11.4%) of these patients discontinued the study.
In the placebo group there were 2 gastrointestinal disorders, one mild with possible relation to the study medication and one severe which was rated as definitely related to the study medication. Further, 3 moderate or mild cases of nausea with possible or probable relation to the study medication and one case of mild nycturia and dry skin each with possible relation to the study medication and finally one case of moderate urinary infection with no relation to the study medication. 2 (4.5%) of the patients of the placebo group discontinued the study due to adverse events.
All the above mentioned patients completely recovered without sequelae.

DISCUSSION AND CONCLUSION

The golden standard in the treatment of lymphoedema is the combined decongestive therapy (CDT) with manual lymphatic drainage, compression, remedial exercises and appropriate skin care.
In the primary criterion of efficacy, the reduction of the volume, the study failed to demonstrate effectiveness, i. e. there was no substantial additional benefit regarding the volume of the arm in the patients with Wobenzym® therapy as compared with placebo. This stands in contradiction to empirical knowledge and the authors experiences about enzyme treatment.
Three considerations may clarify the problem: has the CDT been so powerful, even over a follow-up period of 6 weeks, that no additional effect of the enzyme therapy could emerge, or, has the follow-up period been to short to show any differences in the groups, or, but this seems to be out of question, is there really no effect on the lymphangiomotoricity? In tissue diseased by a lymphoedema fibrotic changes will developed as sequel of the chronic inflammatory condition, especially in the skin.
The skinfold thickness as a powerful parameter for the severity of lymphoedema could not be improved by the enzyme therapy in general and with statistical significance.
Only in the lower arm and in the hand a medium statistical significance for the test medication could be demonstrated.
These sites are the most affected locations with fibrotic changes in accordance to anatomy of the lymph vessels and the surgical performances of these days (6).
The measurement of the volume is not the only objective criterion scoring lymphoedema. The fibrotic changes as well are influencing the outcome of the lymphoedema treatment.
There are no strong data available about the fibrotic measurements and their influences.
Fibrosis is always the result of an inflammatory process (3,6,12) and so far responsible for the outcome.
Skin infections in the individual case history as well as the influence of chemotherapy are no negligible risk factors developing lymphoedema.
For patients with these risk factors are benefits out of this treatment modality expectable.
Herein, the long term preview regarding the maintenance expects some advantages for the enzyme medication, because the softer the tissue the better a regaining of oedema will be avoided.
On the other hand, the inflammation related criteria show more than small superiority for the Wobenzym® group
Reduced inflammatory tissue conditions are the basis for minimising fibrosis thus preventing further inflammation and infection (11).

Two final conclusions may be:

All in all, the study failed to demonstrate efficacy in oedema-related criteria (most likely due to extensive concomitant physical therapy in all patients) but is demonstrating efficacy of Wobenzym® with regard to inflammation-related criteria:

- The inflammation-related criteria show more than small superiority of Wobenzym®

- For the subgroup "no chemotherapy" the inflammation-related criteria show more than medium-sized superiority of Wobenzym®

It is recommended to verify the results by a new, carefully planned and sufficiently sized study with the inflammation-related efficacy criteria tension and CRP as primary criteria.
Patients with anamnestic chemotherapy should be excluded.
Concerning safety considerations, the results show no substantial difference between treatment with Wobenzym® (7 AEs) or placebo (8 AEs) and are indicating a good tolerability of Wobenzym®.
Further long term (12 months) studies will be needed to verify a potential effect on the volume reduction.
Secondly, more attention should be attracted to the inflammation related criteria.

Name and address of the author:
Renato Kasseroller, MD
Privatklinik St.Barbara, Gefäßzentrum
Rödhammer Weg 91
A 5424 Bad Vigaun

Tel.: +43 6245 8999 622
Fax: +43 6245 8999 8401
Email: kasserolymph@aon.at

LITERATURE

1. Földi M., Lehrbuch der Lymphologie, Fischer Verlag, Stuttgart, 5. Auflage, 2002.

2. Kasseroller R., Kompendium der manuellen Lymphdrainage nach Dr. Vodder und der kombinierten physikalischen Entstauungstherapie, Haug Verlag Stuttgart, 3. Auflage, 2002, 100 – 126.

3. Siems R,. Brenke A., Bayer P., Grünberger T., Grüne K., Cremer E.,Conrady,Schrauzer GN., Therapieoptimierung beim chronischen Lymphödem chirurgisch behandelter Tumorpatienten nach Natriumselenit, Dt ZeitschriftOnkol 26: 128-132,1994.

4. Kuhnke E., Volumenbestimmung aus Umfangmessungen, Fol. angiologica Vol XXIV, 7/8/76.

5. Korpan I., Fialka V., Wobenzym und Diuretikatherapie beim Lymphödem nach Mammaoperation, Wr.Medizinische Wochenschrift,1996, 146, 67-74.

6. LVF - Lymphödemklassifikation des inguinalen und axillären Tributargebietes, Journal f Lymphologie, Nr 2, 2002

7. Keim H et al., Methode zur Milderung der Lymphstauung am Arm nach Behandlung des Mammakarzinoms, Röntgenberichte 1 (1972) 45-50 (1973) 338-340

8. Scheef W., Pischnamazadeh M., Proteolytische Enzyme als einfache und sichere Methode zur Verhütung des Lymphödems nach ablatio mammae, Medwelt, 35, 1984, 1032-1033

9.Kasseroller R.,Sodium selenite as prophylaxis against erysipelas in secondary lymphoedema, Anticancer Research, Vol 18, No 3C 5/6 1998, 2227-2231

10. Schrauzer GN, Kasseroller R., Treatment of secondary lymphoedema with physical decongestive therapy and sodium selenite, a review, American Journal of Therapeutics 7, 273-279,2000.

11. Weissleder H., Schuchhardt Chr., Lymphoedema, Diagnosis and Therapy, pathophysiology, Viavital Verlag Köln, 2000, 35-49.

12. Bankl H. Pathologie der Kreislauforgan, in Holzer, Spezielle Pathologie des Menschen, urban und Schwarzenberg,74

THE EUROPEAN JOURNAL OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

XXIX Congress of G.E.L.

European Group of Lymphology, 12-14 June, 2003, Malmö, Sweden

Dear Colleagues and Lymphologists,
The Department of Plastic and Reconstructive Surgery will organize the XXIX G.E.L. Congress of the European Group of Lymphology under the patronage of the Medical Faculty, Lund University and Malmö University Hospital, Region Skåne.
The discovery and delineation of the lymphatic system is ascribed to Olof Rudbeck of Sweden, who in 1652 at the age of 22, submitted his medical thesis "De Circulatione Sanguinis" and the following year published the discoveries concerning the "vasa serosa". Therefore the choice of Malmö, as the venue for this meeting confirms, with our great satisfaction, the focus on our Department to the development of Lymphology above all in the surgical field. Next 12-14 June 2003, the most renown scientists of European Lymphology will gather in Malmö to debate and compare upon the topical subjects concerning lymphedema, the lymphatic system and their several multi and interdisciplinary correlations. This season is the best time of the year to visit Sweden with its exotic light summer nights and pleasant climate. We are waiting for You in Malmö for this special occasion, remaining at Your complete disposal for any scientific information and for any suggestion that can make your stay even more pleasant in our dynamic and beautiful city.
On behalf of the Organizing Committee I salute You: "Välkomna!"

Håkan Brorson, MD, PhD
Congress President

Congress President: Håkan Brorson, MD, PhD (Malmö-Lund)
Honorary Presidents: Sten Jacobsson, MD, PhD (Malmö), Iwona Swedborg, MD, PhD (Stockholm)
Local organizing committee: Malmö-Lund: Henry Svensson, MD, PhD (Professor and Head, Department of Plastic and Reconstructive Surgery), Håkan Brorson, MD, PhD, Magnus Åberg, MD, PhD, Ingrid Tengrup, MD, PhD, Karin Johansson, PT, PhD, Karin Ohlin, OT, Gaby Olsson, PT Stockholm: Leif Perbeck, MD, PhD, Elizabeth Johansson, PT Falköping: Artur Tenenbaum, MD

Preliminary program and scientific agenda

Preliminary topics and subjects. Primary lymphedema, Secondary lymphedema, Lymphatic imaging, Prevention, Phy-sical treatment, Cancer and lymphedema, Surgery of lymphedem.
Thursday 12 June 2003: Welcome reception (Malmö Town Hall at 7 p.m.).
Friday 13 June 2003: 07.30-08.45 Registration - Jubileumsaulan, Medical Research Center (MFC, Medicinskt forskningscentrum), Entrance 59, Malmö University Hospital (Location: See map; download at top of page).
08.45-17.00 Scientific Program - 18.00-22.00 Canal tour of Malmö and Gala dinner
Saturday 14 June 2003: 08.30-15.30 Scientific Program - 15.30-17.00 General Assembly of G.E.L. (G.E.L. members)

Congress secretariat: Mrs. Marika Bergman - Department of Plastic and Reconstructive Surgery - Malmö University Hospital - SE-205 02 Malmö, Sweden - Phone: +46 40 33 64 88 - Fax: +46 40 33 62 71 - Email: marika.bergman@skane.se - Congress web site at: http://www.plasticsurg.nu
Venue: The conference will take place at "Jubileumsaulan", Medical Research Center (MFC, Medicinskt forskningscentrum). Entrance 59, Malmö University Hospital, Malmö

Important days and payment

Abstract: Submission of abstracts: Download (see top of page) the abstract form with all details. Deadline 15 April 2003.
Notification of the decision by the scientific committee: 30 April 2003.
Registration: Print and send the registration by airmail, Email or fax to the Congress secretariat (see Congress secretariat) together with confirmation of payment.
Members of G.E.L who have paid the 2003 annual dues send a copy of this payment together with the registration. Deadline for registration - Early registration fee before 30 April 2003 - Late registration fee after 30 April 2003 - Onsite registration is possible - No refund after 10 May 2003
Confirmation of registration: After 10 May 2003 we confirm the receipt of registration fee. Please bring the confirmation of registration to the registration desk when you register!
Payment: Registration fees in Swedish Crowns (SEK)
Members of G.E.L.
1. Members of G.E.L. who have paid the 2003 annual dues do not pay registration fee.
2. Members of G.E.L. who have not paid the 2003 annual dues:
1 400 SEK (paid before 30 April 2003); 1 900 SEK (paid after 30 April 2003); 2 400 SEK (on site registration) - No refund will be made after 10 May 2003
Overseas delegates: All payment should be forwarded in Swedish currency (SEK). Bank to Bank transfer (overseas delegates). The total amount (free of any bank transfer charges) to: BANK: Swedbank, SE105 34 Stockholm, Sweden - ACCOUNT HOLDER: European Group of Lymphology Congress - IBAN (International Bank Account Number): SE 8280 000 821 499 746 081 505 - SWIFT ADDRESS: SWEDSESS
Please note the following information on your payment: G.E.L. Congress, June 12-14, 2003; Your and accompanying person's name.
Admission to the Congress is allowed only if the Organizing Secretariat has received the Registration fee. Delegates who have made late payments should bring a copy of the bank transaction to the Congress. Onsite registration is possible (cash (SEK) only).

Håkan Brorson, M.D., Ph.D.
Consultant Plastic Surgeon - Department of Plastic and Reconstructive Surgery- Malmoe University Hospital - SE-205 02 Malmoe - Sweden
Mail: brorson@plasticsurg.nu - Homepage: http://www.plasticsurg.nu/
Phone: +46-40-33 10 00 work; pager 2848 - Phone: +46-451-83 838 - home - Fax: +46-40-33 62 71

THE EUROPEAN JOURNAL
OF
lymphology
and related problems
VOLUME 10 • No. 37-38 • 2002-2003

"First European Summer Course on Vascular Lymphatic Diseases"

Organized By the " European School (or Academy) of Lymphology (EAL or ESL)" From the Saturday 26th of July (at 08.00 am) to the Saturday 3rd of Augustus 2003 (at 6.00 pm),

IN BRUSSELS (BELGIUM)

Opened to physicians (vascular surgeons, angiologists,...) and other specialists (physical therapists, nurses, health care professionals...), either interested in lymphology, or for whose the practice includes lymphology

Program of the Course will include:

- The embriology of the lymphatic system (vessels and nodes), Microanatomy of the lymphatic system (from the interstitial spaces to the vessels and nodes), Innervation, hormonal receptors, nervous and/or hormonal regulation of the lymphatic system, Physiology and pathophysiology of the lymphatic system (including microcirculatory aspects), Healing (processes) of lymphatic vascular system , Angiogenic factors and histological markers of the vascular lymphatic system, Effects of irradiation on lymphatic system, The immune system and the lymphatic system, Macroanatomy of the lymphatic system (vessels and nodes, of the upper limbs and lower limbs, of the head and neck, of the anterior and posterior chest wall, of the anterior abdomen and pelvis, of the inferior part of the back).
- Presentation of the great vascular lymphatic diseases, Epidemiological data about vascular lymphatic diseases, Clinic and genetics of the inherited vascular lymphatic diseases, Chromosomes abnormalities in vascular lymphatic diseases, Clinical diagnosis and differential diagnosis of the limbedemas, of the various edematous situations related to vascular lymphatic diseases, Post-therapeutic upper limb edemas, Post-therapeutic lower limb edemas, Post-therapeutic edemas of the face, Chylous reflux, chylorreas, chylurias,... (clinics, epidemiological data, complications and treatments), Diagnosis and treatments of parasitous lymphatic diseases, Limbedemas related to neurological diseases, Diagnosis and treatment of infectious diseases complicating vascular lymphatic diseases of the limbs, Diagnosis and treatment of edematous situations of the genitalia related to vascular lymphatic diseases, Diagnosis and treatments of dermatological diseases (benign and malignant) complicating vascular lymphatic diseases, The preventions of post-therapeutic, secundary limbedema related to lymphatic diseases, European consensus over definitions of limbedemas and of vascular lymphatic diseases.
- The techniques for imaging and investigating the lymphatic system (CT, RMN, Conventional RX, vita blue dyes techniques, X-ray lymphangiography, anatomical tetchniques, Nuclear Medicine techniques, lymphoscinitgrapies, PET,...),
- The treatments of the pathological situations related to lymphatic vascular diseases (Treatments of vascular lymphatic syndromes : Treatments of Limbedemas , Evaluation methods of treatments of edemas, Psycho-pathological considerations about patients with lymphatic vascular diseases, Pharmacological treatments of edemas related to vascular lymphatic diseases (drugs, " heat ",...), Physical treatments of edema related to vascular lymphatic diseases (manual lymphatic drainage, pressotherapy, bandagings, stockings,...) with Basis, Presentation of the various therapeutic " schools " (Foeldi's school, Leduc's school, Vodder's school) : Surgical treatments of lymphedemas).
- Economical (and Ethical) Aspects of the Treatments of Limbedemas (Cost of the proposed physical treatments and surgeries for limbedemas and National regulations of reimbursements, especially for the proposed physical treatments : Presentation of the compared costs for the various surgeries in the European countries followed by one round table and public discussion with participation of the listed surgeons :

With the participation (* confirmed at the 1/01/2003) of the followings (Mrs and/or Professors and/or MD and/or PT and/or PhD) from France, Belgium, Germany, Italy, Netherlands, Austria, Czech Republik, Great Britain, Poland,...:
Alliot, Baumeister, Beaujean*, Behar*, Becker*, Belgrado*, Biscompte*, Boccardo, Bourgeois*, Campisi, Cluzan, Corda, Della Toffola, Eliska*, Flour, Foeldi*, Folliguet*, Gerard*, Hidden, Kasseroller*, Leduc A et O*, Lemort, Lievens, Marchal, Matassi, Michelini*, Moereman, Mortimer, Nieuborg*, Oslzewski, Pflug*, Picard*, Pissas*, Philipsson, Riquet*, Schnmutz*, Thibaut*, VanVooren*, Vikkula, Wahl*, Wautrecht*, Willeputte*, Wigg*,...
Cost of the course (organized for at least 30 participating people) : 500 Euros.

For further informations and/or registration, contact local organizing committee and secretariat:
Dr Pierre BOURGEOIS: E-mail: pierre.bourgeois@bordet.be, Fax :32-2-5413224 or 32-2-4101636
Mr Jean-Pol BELGRADO : E-mail : belgrado@ulb.ac.be

Bauerfeind Scientific Phlebology Award of the IUP

Application Guidelines

Name : _____
Date of birth : _____
Nationality : _____
Specialised in : _____
Address at work: _____
Private Address: _____
Telephone: _____ Area code: _____ att. Number _____
e-mail: _____

1 Introduction

The International Union of Phlebology in co-operation with Bauerfeind Phlebologie GmbH & Co. KG invites applicants for the **Bauerfeind Scientific Phlebology Award of the IUP.**
An award of 20.000 Euro is available on a biannual basis.
The award will enable young scientists to put their study theory on compression therapy into a practical application. This thereby enhances the variety of treatments available, raises the awareness on phlebology and associated conditions and offers future prospects to patients.
Assessment will be made on the following:

2 Technical Part

2.1 Study protocol

A convincing study protocol for a scheduled project, related to compression therapy has to be submitted.

2.2 Scientific basis

The provided study protocol should be based on a minimum of three published papers within the past five years.

3 Formal Part

3.1 Curriculum vitae

The applicant should submit a full written C.V. together with any relevant achievements within his / her professional career, enclosing copies of published papers.

3.2 Age

The applicant should not be older than 45 years.

3.3 Closing date

Please provide us with two copies of your application, written in English by 31 May 2003.

4 International Jury

The board is comprised of the following professionals:
Hugo Partsch, MD (Austria), Albert-Adrien Ramelet, MD (Switzerland), H. A. M. Neumann, MD (Netherlands), Horst Gerlach, MD (Germany), Jorge Ulloa Dominguez, MD (Colombia), Robert A. Weiss, MD (U.S.), Hans-Jürgen Thomä PD (Germany)

5 The Award

The 20.000 Euro Award will be divided into two instalments:
The first 10.000 Euro will be presented at the interim Congress of the IUP in San Diego in August 2003.
The second 10.000 Euro will be presented on completion of the project, which has to be within an 18 months period.

6 Contact

Bauerfeind Phlebologie GmbH & Co. KG
Mrs. Annegret Heinz
Weissendorfer Straße 5
07937 Zeulenroda
Germany

Tel.: +49 (0)36628/ 66-0
Fax.:+49 (0)36628 /66-378
E-mail: aheinz@bauerfeind-phlebologie.de

In Memoriam

Professor AUREL KAUFMANN (1925 - 2002)

On Wednesday the 14th of August 2002, Professor Aurel Kaufmann passed into eternity with the certainty that he had fulfilled his mission.
A complex personality, a restless and innovative mind, Professor Aurel Kaufmann dedicated his life to his patients, his teaching career, the promotion of scientific research and the organization of the Romanian Society of Angiology and Peripheral Vascular Surgery. He was born on the 27th of August 1925 in Braila. He graduated the Faculty of General Medicine of the Cluj University in 1951. He was head of the Surgical Clinic II of Cluj-Napoca between 1980 - 1991 and emeritus member of the Romanian Academy of Medical Sciences since 1993. He founded the Romanian Society of Angiology and Peripheral Vascular Surgery, he was its first president and then elected honorary president. In 1991 he founded the Balkan Society of Angiology and Vascular Surgery. He was Editor-in-chief of the Romanian Journal of Angiology and Vascular Surgery and member of the editorial boards of the following journals: The European Journal of Lymphology, Patologia Vascular (Madrid), Romanian Journal of Hand and Reconstructive Microsurgery, Clujul Medical.
He performed the first lymphography in a human in Romania, using a water-soluble contrast agent (1962), he personally devised an intralymphatic injection apparatus, patented in 1966, and published the first monograph on the exploration of lymph vessels Limfografia in 1970.
In 1983 he set up the first Experimental Laboratory of Microsurgery in Romania. He established a Section of Microsurgery within the Romanian Society of Angiology and Peripheral Vascular Surgery, thus creating the conditions for initial training in microsurgery in Cluj as well as the framework for converging all the individual preoccupations in the field towards a national learned society of microsurgery.A well-known general surgeon, his field of excellence was peripheral vascular surgery, which won him a well deserved national and international prestige. His enthusiasm was infectious and gathered numerous disciples round him. He contributed in the course of decades to the formation for the surgical specialities of many gene-rations of physicians and residents. He educated them in the spirit of compassion for the suffering, honesty, professional responsibility and mutual respect. His work and contribution to the development of vascular surgery was rewarded by academic titles and he was ce-lebrated by the scientific and learned societies and professional associations. His contribution to the prestige of the Cluj Medical School won him first-rank diplomas and medals from the Romanian Government and Presidency.
The most precious recognition, however, will remain the thoughts and feelings of appreciation and gratitude in the minds and hearts of all those to whom he dedicated himself.

Constantin Ciuce

Une page d'hisoire de la lymphologie est tournée: le Professeur Marceau SERVELLE Président d'Honneur du Groupement Européen de Lymphologie (G.E.I.) nous a quittés.

C'est avec une très profonde tristesse que nous est parvenue la nouvelle du décès de notre President d'Honneur, Maître et ami, Marceau SERVELLE.

Marceau SERVELLE est né le 28 avril 1912 a AUXONNE où il effectue ses études secondaires. Puis il choisit la curriére méèdicale. Il est admis à l'École militaire du corps de santé de LYON. Interne de chirurgie à STRASBOURG entre 1938 et 1939, il porsuit son internat à LYON, pouis à PARIS, élève de René LERICHE dont la grandeur chirurgicale et la personnalité vont le marquer à la vie. Il est attaché à l'hôpital St. Antoine dans le service du professeur BERGERET et réalise la première lympholgraphie. En 1951 il réealise la première transplantation rénale (greffon prélevé sur un condamné). La prouesse technique est reconnée et le succès immédiat assuré. Le greffon sera rejeté quelques semaines plus tard, les problèmes immunologiques n'étant pas encore maitrisés....La même année, assisté du Professeur O'NEIL, il réalise la première mitrale. En 1955 il est nommé Chef de Service de Chirurgie thoracique et cardiovasculaire à l'Hôpital St. Michel à PARIS. L'activité chirurgicale s'intensifie et les publications jalonnent la carrieère de Marceau SERVELLE: canal artériel, coarctation de l'aorte, circulation extracorporelle greffe coronaire, tétralogie de Fallot, communication inter-auriculaire, communication interventriculaire. Il est l'auteur de centaines des publications et de plusieurs ouvrage. Il porsuit san relâché son actvité chirurgicale, ses études, sa recherche et il néglige absolument pas le maintien de sa formation permanente qu'il cutlive auprès de ses amis américains BLALOCK, WALLACE, O'NEIL. Dans le domaine de la lymphologie il apparaît comme le seul véritable pionnier de son temps. Chirurgien et chercheur visionnaire il n'hésite pas à proposer des concepts parfois hétérodoxes qui aujourd'hui apparaissent come l'évidence, que ce soit par les maladies malformatives lymphatiques, thoraciques ou digestives ou pour le lymphoedème des membres, pour le syndrome de Klippel Trenaunay. La lecture de ses travaux, en particulier des deux ouvrages: pathologies vasculaires et les chyllferes sont une merveille de réalisme clinique. Alors que plusieurs éléments connus depuis, manquaient au puzzle de son raisonnement, il n'a pas hésité à franchir le pas et à sortir des sentiers battus. C: PAPENDIECK, ancien Président de l'I.S.L. n'hésite pas à substituer à l'ancien nom du syndrome, celui de KIPPLER TRENAUNAY SERVELLE. C'est une des raisons qui nous l'a fait proposer comme Président d'honneur du Groupement Européen de lymphologie (G.E.I.) au cours justement de IX congrès de la Socieété Européenne de Lymphologie à GRENOBLE. Cette vie professionnelle bien remplie n'exclut pas loin s'en faut une vie civique personnelle, familiale et amicale d'une extraordinaire rareté. Chevalier de la Légion d'Honneur, Croix de guerre en 1940, il étatit Cavalière de la République italienne pour les nombreux service rendus aux multiples patients italiens qu'il a opérés. Sa famille était toujours associée à son développement professionnel. Madame SERVELLE à qui nous présentons toutes non condoléances, nous a fait l'honneur de nous accueillir, avec nos amis Albert LEDUC, Corradino CAMPISI, Pierre BOURGEOIS et Cristobal PAPENDIECK un soir de septembre 1991. Ce soir là nous apprenions la terrible nouvelle qui guettait un de non amis commun Isidoro CAPLAN. La memoire du Professeur Marceau SERVELLE restera inscite en lettres d'or dans l'hisoire de la lymphologie. Son esprit de pionnier continuera de souffler longtemps. Madame le Professeur G. HIDDEN, ancien Président du G.E.L., m'a confessé qu'une parte importante de son goût de la lymphologie venait justement de la lecture qu'elle avait eue des travaux de ce maître. Ques les jeunes générations s'investissent dans la lymphologie! Ils découvriront sur leur chemins les travaux fondamentaux de Marceau SERVELLE.

Prof Alexandre Pissas

TEX-SAN

GAUZE BANDAGES

FIXATION BANDAGES

UNIVERSAL BANDAGES

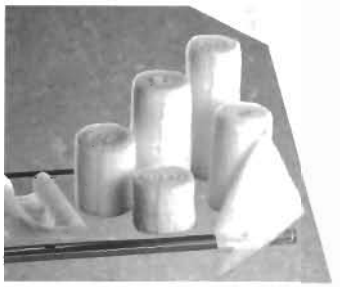
COMPRESSION BANDAGES

ZINC-OXIDE BANDAGES

ZINC-OXIDE AND ITTIOLO BANDAGES

ADESIVE BANDAGES

SOFTEX
MONOSTRETCH ELASTIC BANDAGE FOR DRESSING

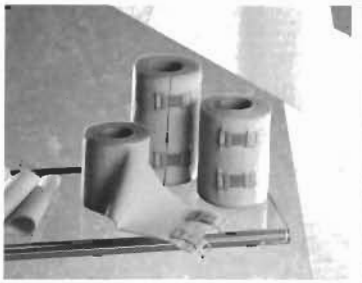


Sizes: 4 - 6 - 8 - 10 - 12 cm (width)
4 meters long (when fully stretched)
Composition: 70% cotton, 30% polyester

PRODUCT
Permanent unidirectional elastic bandage; stretch range 60% ±10% in length (starting from rest). Aerated. Absolutely tolerated by the skin.

INDICATIONS
To be used for light bandages for dressing, for protection on contusions and hematomas, for generic bandages with light compression. Recommended for direct use by patient.

TEXADUR
MONOSTRETCH ELASTOCOMPRESSIVE BANDAGE

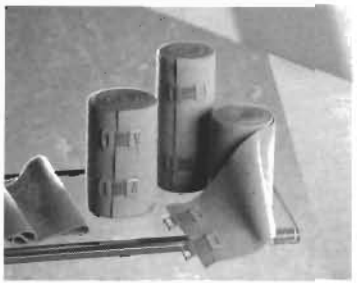


Sizes: 6 - 8 - 10 - 12 cm (width)
5 meters long (when fully stretched) 40%
Composition: 62% cotton, 38% polyamide

PRODUCT
Permanent, very high compression unidirectional elastic bandage; stretch range 60% ± 10% in length (starting from rest). Aerated.
Absolutely tolerated by the skin.

INDICATIONS
To be used for compression support bandages for prophylaxis of edema and phlebostasis, treatment of lymphatic edema, treatment of phlebeurysma, support bandages for dislocations, sprains, fractures and sports injuries.

BENDATEX
MONOSTRETCH ELASTOCOMPRESSIVE BANDAGE



Sizes: 6-8-10-12-15-20 cm (width)
5 and 7 meters long (when fully stretched)
Composition: 45% cotton, 41% modal, 8% polyamide, 6% dorlastan

PRODUCT
Permanent unidirectional elastic bandage; stretch range 180% ±10% in length (starting from rest). Highly aerated. Absolutely tolerated by the skin.

INDICATIONS
To be used for medium-light compression bandages for prophylaxis of edema and phlebostasis, treatment of lymphatic edema, treatment of phlebeurysma, compression bandages after surgery, bandaging of joints, support bandages for dislocations, sprains, fractures and sports injuries.

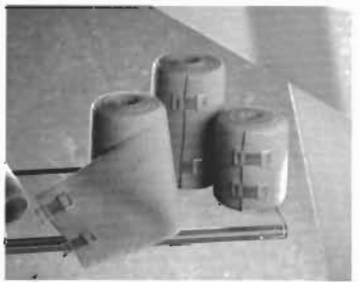
BENDATEX XF
MONOSTRETCH ELASTOCOMPRESSIVE BANDAGE

Sizes: 6-8-10-12-15-20 cm (width)
5 and 7 meters long (when fully stretched)
Composition: 41% cotton, 37% modal, 14% polyester, dorlastan 8%

PRODUCT
Permanent, high compression unidirectional elastic bandage; stretch range 180% ± 10% in length (starting from rest). Aerated.
Absolutely tolerated by the skin.

INDICATIONS
To be used for high compression support and drainage bandages for prophylaxis of edema and phlebostasis, treatment of lymphatic edema, treatment of phlebeurysma, compression bandages after surgery, bandaging of joints, support bandages for dislocations, sprains, fractures and sports injuries.

BENDATEX BLF
MULTISTRETCH ELASTOCOMPRESSIVE BANDAGE

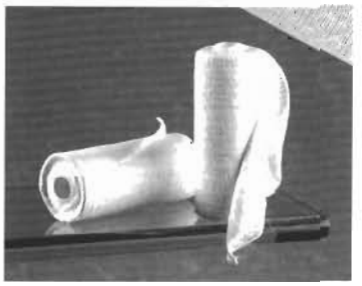


Sizes: 8 - 10 - 12 cm (width)
5 and 7 meters long (when fully stretched)
Composition: 42% cotton, 37% modal, 11% polyamide, rubber 10%

PRODUCT
Permanent, high compression omnidirectional elastic bandage; stretch range 180% ± 10% in length, 60% ± 5% in width (starting from rest).Highly aerated. Absolutely tolerated by the skin.

INDICATIONS
To be used for high compression support and drainage bandages for prophylaxis of edema and phlebostasis, treatment of lymphatic edema, treatment of phlebeurysma, compression bandages after surgery, bandaging of joints, support bandages for dislocations, sprains, fractures and sports injuries. Particularly indicated for bandaging of joints.

ZINCOSAN
NON-ELASTIC AND ELASTIC ZINC-OXIDE BANDAGE



Zincosan non elastic
Sizes: 7,5 - 8 - 10 cm (width)
5 - 6 - 7- 10 m
Composition: 100% cotton, Hypoallergenic

Zincosan elastic
Sizes: 7,5 - 8 - 10 cm (width)
5 and 10 meters long (when fully stretched)
Composition: 67% cotton, 33% polyamide Hypoallergenic

PRODUCT
Elastic gauze bandage impregnated with zinc-oxide paste.

INDICATIONS
Treatment of phlebothrombosis, venous ulcers, varicose veins, eczemas, in the therapy of sport and work traumas, after-care of fractures and articulation surgery. Ideal for anti-inflammatory bandaging and to support sprains, dislocations and bruising.

INSTRUCTIONS FOR USE
Zincosan Elastic is to be used together with compressive or adhesive bandages. Store at a max. temperature of 25°C. Non-sterile. Class 1 product.

FILMAR

FILMAR srl
Strada Leinì, 22
10072 Caselle Torinese (TO) ITALIA
Tel. +39 011.996.1080 - 011.996.1525
Fax 011/991.42.71
e-mail: filmar@fileita.it
www.filmarsrl.com