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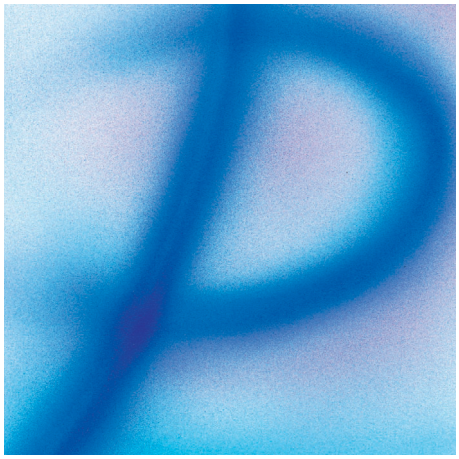

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AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous disease.

The aim of *Phlebolymphology* is to provide doctors with updated and interesting information on phlebology and lymphology written by well-known specialists from different countries worldwide.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in the EMBASE database in 1998.

Phlebolymphology is made up of several sections: editorial, articles on phlebology and lymphology, news, review, and congress calendar.

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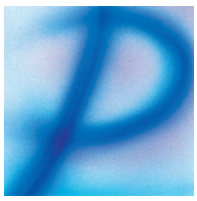

IN MEMORY OF PROFESSOR J.A. JIMENEZ COSSIO

We would all like to die in the arms of people who loved us. Doctors devoted to research and conferences have two families: the wife and children on one hand, and the international scientific stage on the other.

The accusation of neglecting family because of work and conferences is quite frequent among doctors and often well-founded. My friend Jimenez Cossio was a rare example of the balance between the man with his affections and the scientist. Fate chose for him a death in the arms of friends and colleagues on his natural stage, a Congress in Lisbon. He died on the field just like his historical ancestor El Cid.

His career was brilliant: he graduated in Madrid, his adopted city, in 1963, and was Head of Angiology and Vascular Surgery Department since 1978, and Professor in the Faculty of Medicine of Madrid.

Though interested in all the branches of angiology and vascular surgery, which share the same roots in Spain, he always devoted himself to lymphology with the perspicacity of the pure researcher who, through surgeon's pragmatism, never lost sight of concrete implications of research.

He was President of the Spanish Club of Lymphology and of the 16th World Congress of Lymphology, President of the Spanish Society of Angiology and Vascular Surgery in 1989, Member of 30 National and International Societies of Vascular Pathology, author of books and scientific papers published in international journals, and recently President of the World College of Vascular Diseases.

An untiring and quick worker: proposals of research and organizational work were immediately followed by plans. Connection between thought and action was extremely brief, if not immediate.

Curious about the world, he followed its evolution through research, even in its most innovative aspects, such as computer science, with ease and reliability.

He was one of the first to bring vascular pathology onto CD-Rom, involving colleagues from all over the world in this project. His links outside Spain were many and extensive; though he kept a particular relationship with South America, due to language and culture, he was familiar with English-speaking and European countries too.

I think he was not competitive, and he basically loved cooperation among colleagues. He used to whisper the invitation to do something with a charming smile.

His affectionate and quiet character made him a well-accepted personality, and a reliable and cooperative friend to us all. To grow up and take on high-responsibility tasks and, in the same time, to keep the spirit of the game and enthusiasm, is a gift of few people.

His death leaves a great gap in everybody's soul, but his smile and his look straight to the future will help us serenely face these times full of technology, and understand that research can be carried out with a smile even if with a rigorous method.

Prof Claudio Allegra

Mechanisms of onset of chronic venous insufficiency (CVI)

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The pathophysiology of CVI remained relatively obscure until recently, but recent advances relating hemodynamic disorders to cell biology have shed light on how its mechanisms interlink. CVI may be due to hereditary abnormalities of vessel walls or tissues, or appear to be secondary to deep vein thrombosis. However, it is usually apparently primary, with which this analysis is concerned. The cause of CVI is then related to a circle of actions, including the progression of venous hypertension (VH), leading to disturbances of blood flow and venous stasis. These two factors act on the *walls of main veins* and cause varicosities, and on the *microcirculation*, where they cause edema and ulcers.

I - VENOUS HYPERTENSION AND VENOUS STASIS

Intravenous hydrostatic pressure is high in humans: when standing, venous pressure at the ankle is 85 mm Hg and should normally drop to 45 mm Hg when walking because of the peripheral heart effect - a system incorporating contraction of calf muscles, the action of venous valves, the arteriolo-venular reflex and the action of the diaphragm. This fall in blood pressure enables blood to ascend via lower-limb veins and return to the heart. This is nevertheless a regulatory system required because of the upright position, unknown in animals *(Figure 1)* and which easily deteriorates with advancing age.

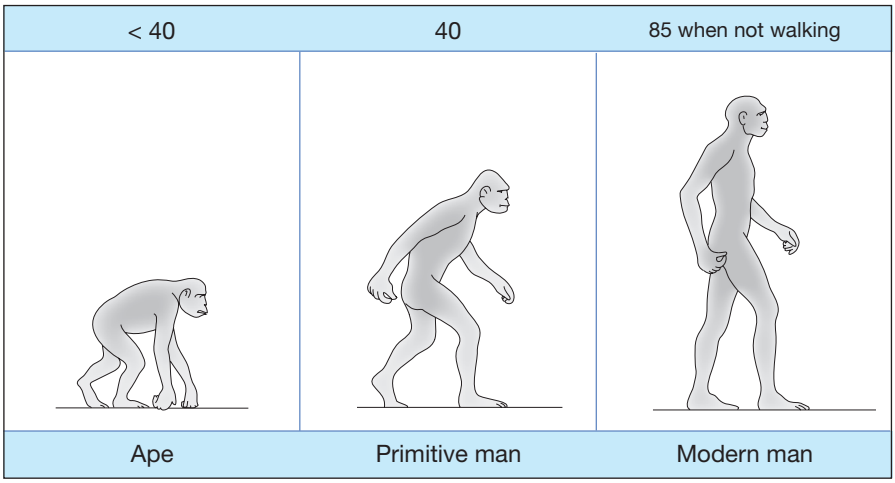


Figure 1. Ankle venous pressure (mm Hg).

CVI and venous pressure

In CVI, venous pressure remains high and causes venous stasis in the lower limbs, with distal gravitational force active as far as the microvenules of the skin of the ankles and feet. Evidence of this disorder is found by Nicolaides' measurement of ambulatory venous pressure (AVP) in a vein of the dorsum of the foot. In CVI, it is found to gradually increase and is not corrected by walking. It is accompanied by pain, subcutaneous fibrosis, pigmentation of the skin, and finally ulcers with which it is always associated at high values above 80 mm Hg.

Causes of venous stasis

It is now known that it is essentially *anatomical changes* in veins which are responsible for the persistence of high pressure and the development of venous stasis. Widening and irregularities of main vein walls result in difficult emptying when standing. In other words, it is the development of varicose veins which leads to stasis.

Aggravating factors also play an important role in these anatomical changes.

- Functional abnormalities: reduced *calf ejection fraction* (studied by plethysmography), of fairly late onset, is a highly aggravating factor, related to failure of the muscle pump, especially during bed rest. All the more, *valvular reflux* (detected by Doppler), occurring early, even before valvular incompetence, or late, at various sites in the venous system according to individuals, is a major cause of the worsening of stasis. Reflux is common: it is present in 68% of patients in the saphenous below the knee, in 55% above and in 30% at the saphenofemoral junction. Ulcer patients have severe and multisegmental reflux. Reflux is superficial and deep when edema is present.

- Hemorheological abnormalities: increased blood viscosity and red cell aggregation are present in CVI, in the systemic circulation and even more so in varicose blood vessels. These events are linked to blood levels of large molecules, especially fibrinogen. This is a typical trait of CVI.

Hence anatomical changes of venous wall and the onset of reflux and rheological abnormalities increase with time, according to age, familial hereditary circumstances, pregnancies, and long periods standing. These variable factors create inequality in the clinical manifestations of varicose veins in different groups.

II - MECHANISMS OF DEVELOPMENT OF VARICOSE VEINS

Two mechanisms, *shear stress* abnormality and *hypoxia*, induce transformation and thickening of the venous wall, being responsible for biochemical changes in this structure.

Abnormalities of blood flow shear stress at the wall

When standing, venous return flow easily loses its homogeneity *(Figure 2)*. Because of pulsations which flatten then

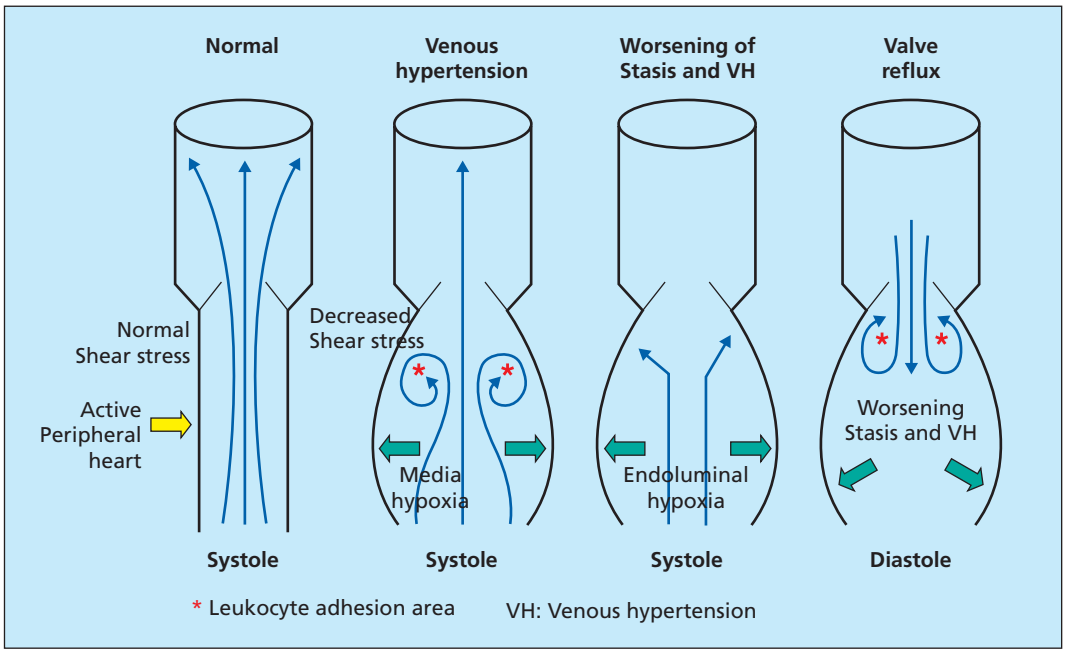
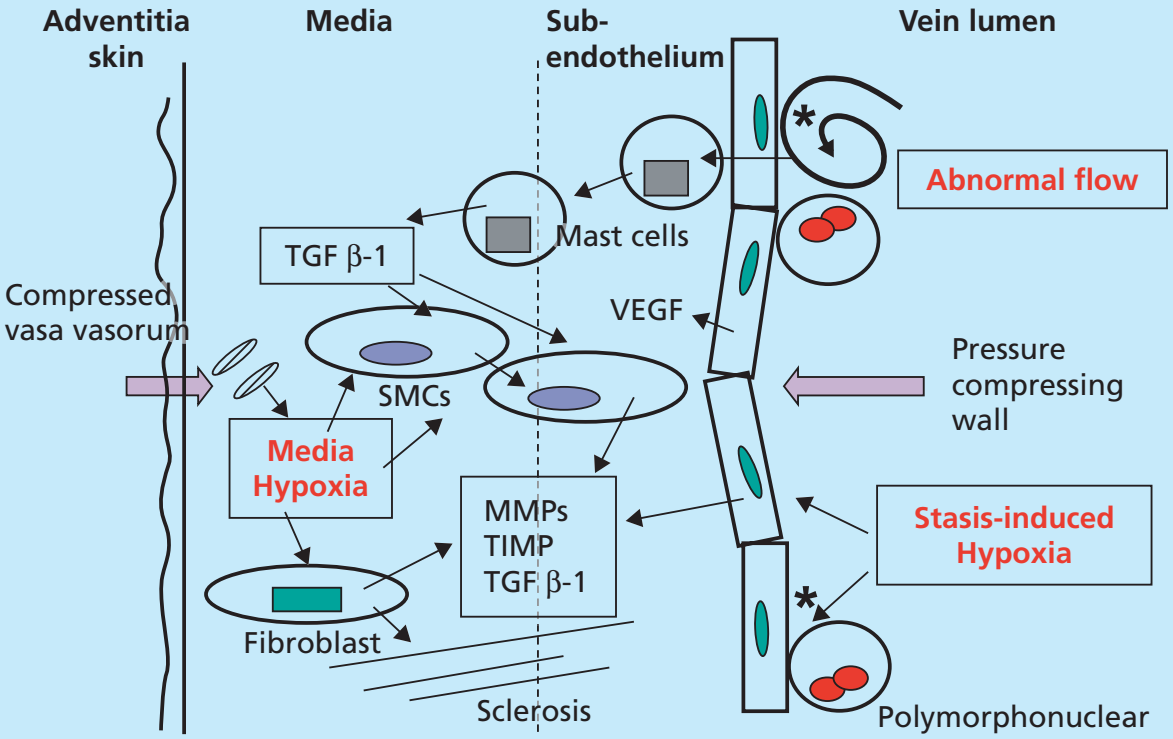


Figure 2. Abnormalities of venous return circulation due to venous hypertension, prolonged stasis, and reflux.



TGF: *transforming growth factor*; VEGF: *vascular endothelial growth factor;*
MMP: *metalloproteinases*; TIMP: *tissue inhibitor metalloproteinases.* *: *leukocyte adhesion area*
SMCs: *smooth muscle cells.*

Figure 3. Three causative mechanisms and biochemistry of reorganization of the venous wall.

open lower-limb veins, it is often pulsatile or turbulent, and endothelial surfaces in particular *lose the influence of shear stress* (5 to 10 dynes/cm^2 instead of 20 to 30). This impairs mechano-transduction, the endothelium activates, opens ionic channels, decreases its nitric oxide (NO) production, increases that of endothelin 1 (ET1) and of plasminogen activator inhibitor (PAI-1). The endothelium in these regions produces cytokines and growth factors, and expresses adhesion molecules. Areas of *slowed leukocyte circulation* are created, especially in subvalvular regions, inducing subendothelial leukocyte transit. Macrophage monocytes and mast cells then supply the wall with the growth factors and enzymes, forming the biochemical basis of varicose veins (see below).

Venous wall hypoxia

When standing, the venous wall is exposed to two hypoxic situations *(Figure 3)*. Because of centrifugal pressure due to the weight of the blood column, the *vasa vasorum* of the media and adventitia are crushed by the skin. This leads to *hypoxia of the media*, activating and differentiating smooth muscle cells (SMCs) and activating fibroblasts. During prolonged periods standing and immobile, there is demonstrable and measurable *hypoxia by endoluminal stasis*. It is also an activation factor, now of the endothelial lining. It is nonetheless transitory, even in patients with developed varicose veins. It is active in zones of slowed circulation, under valves, leading to the expression of leukocyte adhesion molecules, also producing cytokines, growth factors and adhesion molecules.

Biochemistry of varicose wall lesions

Because of abnormal flow, medial hypoxia, and endoluminal hypoxia, growth factors, essentially TGF β-1, are produced in or carried to the wall *(Figure 3)*. They are transported by mast cells and produced in part by activated endothelium and SMCs themselves. The latter, dedifferentiated to secretory cells, migrate to the subendothelium, which

they thicken. Fibroblasts multiply and secrete more zinc-dependent metalloproteinases (MMPs) than their TIMP inhibitor and hence destroy the matrix, in particular elastin, and construct meshes of fibrosis. VEGF, also produced in excess, participates in these disorders and in vascular neogenesis.

Varicose veins

In short, the wall becomes very thick and disorganized, with alternating zones of fibrosis and highly cellular regions. Scanty elastin explains highly increased distensibility. Transformed SMCs are less contractile. As this damage progresses, abnormalities of flow, pressures, and hypoxic situations accentuate, instigating a vicious circle of action. These events are also painful and accompanied early by feelings of *heaviness*, *pins-and-needles*, *and restless legs*. Venous disease is symptomatic as soon as the mechanism of wall damage comes into play.

Biochemical progression markers can be identified in systemic venous blood, also due to changes in the microcirculation. The presence of high levels of PAI-1 is fairly specific to CVI, found in venous blood and constant when there are cutaneous trophic problems. Rheological abnormalities and raised PAI are specific findings in CVI.

III - MICROCIRCULATORY DISTURBANCES

Raised venous pressure downstream creates microcirculatory stasis. Microvessels react to injury via mechanisms similar to the downstream vein. In CVI, this concerns distal, tibial, and retro- or pre-malleolar skin vessels. Venules located in skin layers as well as the capillary loop are distended. Edema and ulceration are the main resultant problems.

Effects of cutaneous microcirculatory stasis

The endothelial cells of the so-called postcapillary venules of the skin are physiologically highly active in the following areas: cellular (transit of white cells by expression of adhesion molecules: selectins, ICAM and VCAM), hemostasis von Willebrand factor, tissue plasminogen activator (tPA) and PAI-1 and of inflammation cytokins, chemokins, platelet-derived growth factor (PGDF) type growth factors, vascular endothelial growth factor (VEGF), tumor growth factor (TGF β-1) and basic fibroblast growth factor (bFGF). They also have another fundamental role: vasomotor regulation ensuring the secretion of vasodilator NO and prostacycline (PGI2) and vasoconstrictor endothelin. In addition, NO, by deactivating blood platelets, prevents them from secreting vasoconstrictor thromboxane A2 (TXA2).

- Endothelial activation and creation of perivascular inflammation Hypoxia is related to stasis and low shear-stress (< 10 dynes/cm^2) and gives rise to exuberant endothelial cell activity. The vasodilator component is defective (NO, PGI2). The substances mentioned above enable the inflow of polymorphonuclears (the "white cell trapping" of Coleridge Smith), but also monocytes and mast cells which migrate in the subendothelium. Since microvessels have neither media nor SMCs, this biochemical disorder results in either fibrosis or necrosis of the ulcer (see below).

- Increased capillary leakage. Endothelial activation and adhesion molecules bring into play MAP-kinase-type pathways, allowing the opening of gaps between cells and the leakage of plasma fluids. This results in edema and the deposition of fibrinogen around microvessels (the "fibrin cuff" of Browse and Burnand).

- Hemorheological abnormalities. Hemoconcentration partially explains the increase in fibrinogen, a nonfiltered macromolecule, and hence hyperviscosity and hyperaggregability of red cells. This interferes with the circulation in microvessels and increases the accumulation of leukocytes. Tests correlate with symptoms (feeling of heavy legs).

Consequences of venous stasis

- Capillary maldistribution. From a vasomotor standpoint, NO and PG12 are defective, releasing the effects of vasoconstrictor substances ET 1 and TXA2. There is also production of constrictor oxygenated free radicals because of the breakdown of mitochondrial ATP of hypoxic endothelial cells. This leads to the appearance of avascular skin areas where capillaries are closed (video-capillaroscopy). These areas are hypoxemic (low tc-PO^2) forming the basis of white atrophy and are highly sensitive to changes in temperature and trauma. Alongside these areas, there are on the contrary vasodilated areas rich in edema fluid and compressive (Fagrell compressive edema). Finally, other areas are rich in capillary vessels but deformed, forming a specific microangiopathy.

- Fagrell and Bollinger microangiopathy. Video-capillaroscopy has shown what capillary loops look like: they are deformed, with a glomerular appearance, surrounded by an edematous pale halo. Endothelial cells are multiplied and

"wound into a ball" because of growth factors. Histology is specific: fibrin cuff, accumulation of leukocytes and mast cells, and deposit of hemosiderin derived from lysed red cells, explaining the skin pigmentation sometimes present (brawny dermatitis).

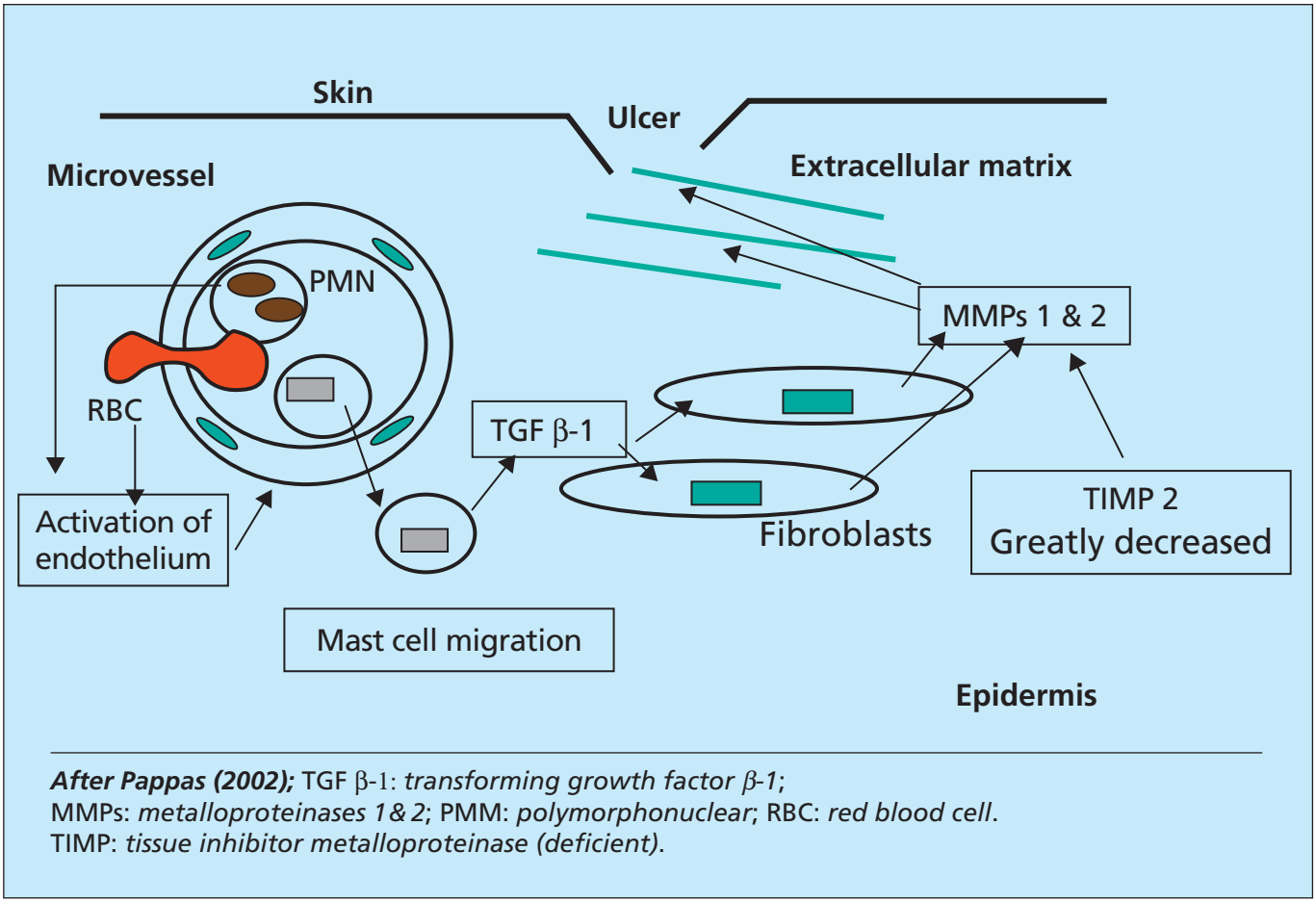
- ***Changes in lymphatic system.*** Lymph vessels are hypertrophic and fragmented, in response to venous pressure and leakage. These lesions play a role in the onset and progression of edema.

- ***Clinically,*** this microcirculatory disorder causes pain accompanying edema, then ongoing skin damage.

IV - PATHOGENESIS OF VENOUS ULCERS

- ***The distal skin: a region requiring constant monitoring.*** The lesions described above form the base of ulcers. Regions most exposed are distal, and malleolar. Inflammation, diabetes, and above all a (sometimes even minimal) blow initiate the ulcer process. Continuous therapeutic attention is essential in this situation.

- ***Cellular and biochemical mechanisms.*** Some theories appear to be secondary: anoxia or "barrier" role of fibrin cuff, Fagrell compressive edema, Bollinger capillary thrombosis. Two processes seem to act, as has been shown recently: accumulation of leukocytes (Coleridge-Smith's white cell trapping), explaining the rich enzyme potential surrounding the microvenule, and the role after migration of monocytes and mast cells, based upon the work of P.J. Pappas *(Figure 4)*. Attracted by chemotaxis linked to perivenular hemorrhagic suffusions, mast cells deliver TGF β-1 at a distance in the subendothelium. Activated fibroblasts supply MMPs 1 and 2 destroying the cellular matrix and opening the ulcer. Pappas has shown the existence of these events at stages 4 and 5 of the CEAP classification, where there is a gradient in TGF β-1 receptor levels and little production of inhibitor TIMP. Fibroblasts may subsequently reverse their role at stage 6, provide inhibition, and revert to their fibrosing function in the healing phase.



After Pappas (2002); TGF β-1: *transforming growth factor β-1*;
MMPs: *metalloproteinases 1 & 2*; PMM: *polymorphonuclear*; RBC: *red blood cell*.
TIMP: *tissue inhibitor metalloproteinase (deficient)*.

Figure 4. Cell biochemistry of ulcer pathogenesis.

CONCLUSION

Study of the mechanisms of lesions at different stages of CVI shows how a hemodynamic disorder, excess weight of the blood column in lower limb veins, gradually causes changes in cellular information, then cellular and biochemical disorders *(Figure 5)*. These lesions are now precisely identified, and explain the development of varicose veins, symptoms, edema, and ulcers. Awareness of them opens the way for therapeutic actions of every type, as well as prevention.

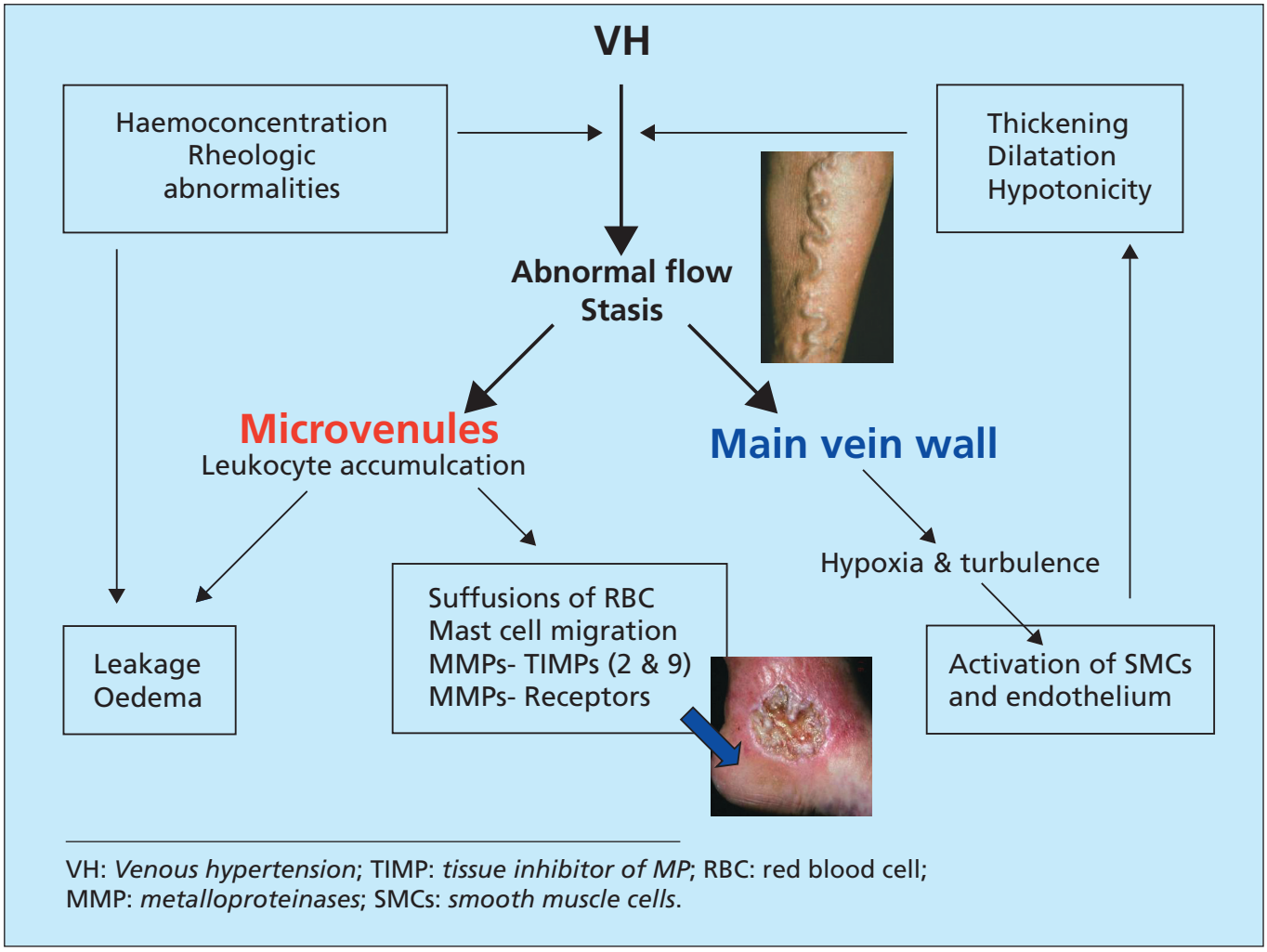


Figure 5. Mechanisms involved in CVI.

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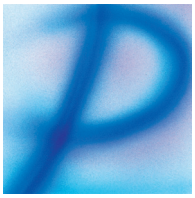

The causes of edema in chronic venous insufficiency

Michel VAYSSAIRAT

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SUMMARY

The edema associated with chronic venous insufficiency (CVI) is the most common type of edema (90%). Like all types of edema, it is defined by an increase in interstitial fluid volume. It differs from other types of edema in terms of its association with microangiopathy of an initially functional and then organic nature, a consequence of the venous stasis which injures the endothelium, impairs endothelial function, and induces severe hemorheological abnormalities. The repercussions at the tissue level are linked to the instigation of inflammatory processes involving numerous chemical mediators, resulting in fibrosis, capillary rarefaction, and hypoxia.

The edema of chronic venous insufficiency is the first sign of microangiopathy. This is why, for very good reason, it is classified as Grade 3 in the CEAP classification, which is made up of 7 grades of increasing severity. Volumetry, a simple investigation, has become a routine screening test for this condition.

INTRODUCTION

Edema is defined as an increase in interstitial fluid volume. It causes an objective clinical symptom frequently encountered in chronic venous insufficiency[1] (CVI) and corresponds to Grade 3 in the CEAP[2] classification (1995) which classifies CVI into 7 grades of increasing severity. It causes disability both in the form of symptoms (pain, heaviness, cramps) and in the form of its esthetic impact, and is one of the factors which diminishes patients' quality of life.[3] It represents 90% of all etiologies of edema. Treatments, whether physical (in the form of compression) or pharmacological, focus on reducing this edema,[4] which is easily measured using a routine investigation.[5]

While most types of edema (cardiac, renal) do not cause pain or ulceration because they only involve functional microangiopathy (impairment of capillary permeability), the type of edema associated with CVI is characterized by its painful nature and its tendency to result in trophic complications because of its association with ischemic organic microangiopathy.

THE MAIN FEATURES OF THE PROBLEM

The type of edema associated with CVI is characterized by an increase in the volume of subcutaneous interstitial fluid in the lower limbs associated with hemodynamic problems caused by venous stasis. Starling's law establishes an equilibrium across the endothelial wall with hydrostatic pressure and oncotic pressure for the intravascular compartment and interstitial pressure for the extravascular compartment.

Mechanism of organic microangiopathy

The hydrostatic forces in the heel and foot range between almost zero in the supine position (a few millimetres of mercury) to 100 mm Hg in the standing position, with this pressure dropping significantly on exertion. The venous circulation in the lower limbs is therefore subject to these considerable variations in pressure which "batter" the upstream venous microcirculation. It is the excessive nature of these constraints and the lack of pressure reduction on exertion caused by the venous reflux of CVI (known as "stasis") which creates the initiating stimulus for microangiopathy and CVI. What follows is simply the establishment of a vicious circle: stasis ➔ impaired capillary permeability ➔ functional microangiopathy compensated by the lymphatic system ➔ decompensated functional microangiopathy (edema) ➔ venular hemorheological abnormalities (endothelium, leucocytes, mediators) ➔ organic microangiopathy with capillary rarefaction (becoming glomerular), hypopigmentation and fibrosis ➔tissue ischemia (white atrophy), hypoxia ➔ opening of arteriovenous shunts ➔ aggravation of stasis and closing of vicious circle.

The type of edema associated with CVI is by no means a sign of the onset of CVI since it reflects the saturation and overflow of the compensatory lymphatic system (silent phase). The severity is not related to the edema itself but to the microangiopathy with which the edema is associated.

THE CAUSES OF EDEMA IN CHRONIC VENOUS INSUFFICIENCY

Macrocirculatory causes

CVI is characterized by venous reflux, the consequences of which constitute stasis. Venous obstruction may also be present, but it is inconstant and often marginal. Varicose veins, venous compliance problems, and deep vein and perforator abnormalities form the basis of CVI, but edema may be absent in compensated varicose disease (Grades 1 and 2 in the CEAP classification). These abnormalities are easily identified by measurement of ambulatory venous pressure.[1,6]

Microcirculatory causes

- Capillary hyperpermeability

Capillary hyperpermeability is a direct consequence of stasis caused by an imbalance in Starling's law in favour of excessive fluid output (water, electrolytes, dissolved substances, proteins). Under normal conditions, there is an excess daily output of around 4 L of dissolved substances. This is the normal capillary output which is usually compensated by lymphatic resorption of an equivalent volume. The type of edema associated with CVI is an extreme symptom of this physiological phenomenon. This mechanism shows how the interactions between the venous and lymphatic systems are closely linked.

Starling's law: a reminder
Starling's law governing capillary exchanges is:

$$Jv = CfC\ (Pc-Pi) - \sigma\ (\Pi c-\Pi i)$$

Jv = Exchange
CfC = Coefficient of filtration
Pc = Capillary pressure
Pi = Interstitial pressure
σ = Oncotic coefficient
Πc = Capillary oncotic pressure
Πi = Interstitial oncotic pressure

This increase in capillary permeability is easily identifiable under fluorescence capillaroscopy by measurement of the pericapillary halo (interstitial fluid) which doubles in size from 80 µ in CVI.[7] As long as the lymphatic system absorbs this excess, the disease remains compensated and there is no edema.

- Hemorheological abnormalities

Hemorheological abnormalities are also the direct consequence of the stasis which perturbs the endothelium and its relations with the components of the blood.

a) Leukocytes

Since the studies conducted by Coleridge-Smith,[8] we know that leukocytes play a preponderant role in this disorder (review in ref 9). Neutrophils and monocytes are activated by venous hypertension with perturbation of certain selectins, integrins and immunoglobulins.[10] In CVI, these leukocytes, which are usually able to move around on the endothelial surface under the influence of an L-selectin which can be measured in the plasma,[11] develop a greater tendency to stick to the endothelium under the influence of an integrin which usually facilitates their perivascular migration. They then remain prisoners within the local microcirculation, and this trapping activates certain physiological inflammatory processes.

b) Red blood cells

Under conditions of stasis, the red blood cells in the capillaries which have become glomerular aggregate[12] and cause capillary thrombosis which is clearly visible in biopsies.

c) Plasma

Patients with CVI show raised fibrinogen levels and therefore plasmatic hyperviscosity which accentuates the stasis. Certain hemostatic mechanisms are also perturbed, one example being the reduction in physiological fibrinolysis.

d) Platelets

Patients with CVI show increased monocyte-platelet aggregation.[13]

- Morphological changes in the capillaries

The capillaries react to these constraints. Capillaroscopy shows a reduction in the number of capillaries per square millimetre, capillary thrombosis, abnormal neogenesis (glomerular capillaries[7,14]) and very uneven distribution with almost no capillaries in some areas (white atrophy).

Impact on tissue

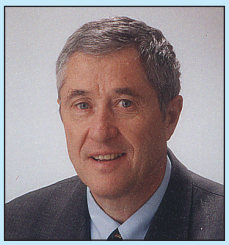
The impact of these disorders on the tissue bring into play multiple chemical mediators related to inflammatory processes (hypopigmentation), resulting in a type of fibrosis called lipodermatosclerosis. The trapping of leukocytes is accompanied by the production of free radicals with their well-known harmful effects which generate edema. In addition, the volume of the edema causes mechanical separation of the capillary from the cell it is feeding, and thus aggravates cellular hypoxia. This multifactorial hypoxia in turn causes vasodilation with opening of shunts which serve to aggravate the existing stasis.

Most of the factors described above interfere with each other, link into complex microangiopathy, and are the direct or indirect causes of the CVI-related edema. We do not have any simple biological markers to quantify this venous stasis which generates edema, but metalloproteinase-9 may be one path worth exploring.[15]

CONCLUSION

The precise causes of the type of edema associated with CVI are now well known. They are part of a greater entity involving hemodynamic abnormalities linked to venous disease which gradually induces complex cutaneous microangiopathy.

These perturbations are usually curable with appropriate venous treatments which have proven their efficacy in both medical and economic terms.[16]



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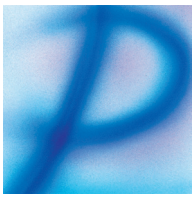

Daflon 500 mg at the very heart of chronic venous insufficiency: results from the meta-analysis presented at the UIP Congress, San Diego, 2003

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Chronic venous insufficiency (CVI) affects approximately 50% of the general population, of whom the vast majority remain untreated.[1-3] Equally, venous leg ulcers (the most severe stage of CVI) are found in more than 1% of the adult general population and in 4% to 5% of patients aged 80 and over.[4] In addition, the *Guidelines of the American Venous Forum* state that the recurrence rate for venous leg ulcer is in fact as high as 25% per year.[5] In patients noncompliant with therapy, several studies have demonstrated a much faster rate of venous leg ulcer recurrence.[6] Therefore, the prevalence of CVI, coupled with the severity of venous leg ulcers and their well-documented deleterious effect on Quality of Life in CVI patients, necessitates a treatment offering a recognized clinical efficacy that is both rapid and long-lasting.

For a number of years, daflon 500 mg, or micronized purified flavonoid fraction (MPFF), an oral phlebotropic drug consisting of 90% micronized diosmin and 10% flavonoids expressed as hesperidin, has been available as a treatment for all stages of CVI. In fact, in recent years, recognition has finally come from international experts of its efficacy in the treatment of CVI patients. Thanks to the results of numerous clinical trials, daflon 500 mg's efficacy in the treatment of venous leg ulcers has been clearly demonstrated.

The efficacy of daflon 500 mg in CVI is due to its comprehensive mode of action, which acts at the heart of the disease, namely the inhibition of leukocyte adhesion. By this mode of action, daflon 500 mg is able to provide relief to CVI patients with the initial symptoms (ie, CEAP stage 0, C0s) of leg heaviness, itchiness, pain, and cramps to those with painful varicose veins (ie, CEAP stage 2, C2), to those with venous leg edema (ie, CEAP stage 3, C3), and finally to those with the most severe stage of CVI, namely venous leg ulcers (ie, CEAP stage 6, C6).

Definitive recognition of an oral pharmacological treatment in venous leg ulcers

Until recently, clinicians used compression therapy with local care as the only treatment for venous leg ulcers. However, the clinical evidence for its efficacy is limited and often related to practices handed down by older clinicians to younger ones. In addition, in the past, American vascular surgeons only ever considered surgical treatment for venous leg ulcers as an effective therapy.

Today, on the other hand, the evidence for adding an oral pharmacological treatment, such as daflon 500 mg, to conventional treatment in venous leg ulcers has been finally recognized by the experts.[5] In the recent 2001 edition of the *Guidelines of the American Venous Forum*, the option of an oral pharmacological treatment was discussed.[5] For the first time ever, the American medical establishment recognized not only another addition to their therapeutic arsenal, but also its efficacy. A whole chapter described the evidence for the efficacy of oral pharmacological treatment in CVI and venous leg ulcers. A large proportion of this evidence, clearly demonstrated by clinical studies, was attributed to daflon 500 mg's efficacy. Moreover, daflon 500 mg is the "only member of the edema-protective group that is effective in the most severe complications of CVI (ie, venous leg ulcers)."

In addition, the 2001 Guidelines for the treatment of CVI from the Italian College of Phlebology[7] recommend that when surgery is neither feasible nor recommended, daflon 500 mg can be used in the treatment of venous leg ulcers.

Earlier in 2003, a review appeared in the world-renowned journal, *Drugs*.[8] This review set out the independent opinions of 14 world experts in the field of phlebology on the therapeutic efficacy of daflon 500 mg in CVI, venous leg ulcers, and hemorrhoidal disease.[2] By reviewing the evidence obtained from well-designed clinical trials, they recognized daflon 500 mg as a well-established phlebotropic and vasoprotective agent which, when used in conjunction with surgery and/or compression therapy, is efficacious in the most advanced stages of CVI.

Proof of daflon 500 mg's unique efficacy in venous leg ulcers

The final confirmation, now recognized by the international experts, of daflon 500 mg's efficacy in venous leg ulcers is provided by the results of a number of clinical trials. Three individual studies (already published) have demonstrated the advantage of daflon 500 mg in association with standard therapy over standard therapy alone[9-11] *(Table I)*. In addition, these results were combined with the results of two other studies (data on file) to form the basis for a "meta-analysis of the venous leg ulcer healing in prospective randomized studies using Micronized Purified Flavonoid Fraction."[12] These results were recently presented at the latest International Congress of the "Union Internationale de Phlébologie" (UIP), San Diego, Calif, and then subsequently published in *Dermatological Surgery*.

No less than 723 venous leg ulcer patients were included in this meta-analysis (making it the largest meta-analysis in venous leg ulcers ever performed). It confirmed that when daflon 500 mg is in association with standard therapy there is improved efficacy in the complete healing of venous leg ulcers over 6 months. In addition, daflon 500 mg

Study	Number of patients	Trial design*	Period (mo)	Control ulcer size (cm)	% complete ulcer healing			Time to complete ulcer healing		
					daflon 500 mg †	Control	*P*	daflon 500 mg †	Control	*P*
Guilhou[9]	107	Placebo	2	≤10	31.8	12.8 ‡	0.028	Shorter time		0.037
Glinski[10]	140	Open	6	<3; 3-6; >6	46.5	27.5 §	<0.05	-	-	-
Roztočil[11]	150	Open	6	≥2; ≤10	64.6	41.2 §	0.004	137 days	166 day §	0.04

Table I. Published studies demonstrating daflon 500 mg's efficacy in ulcer healing.
** Each study included a prospective, multicenter, randomized controlled design*
† daflon 500 mg, 2 tablets daily, in association with standard therapy
‡ Control group: placebo + standard therapy
§ Control group: standard therapy alone

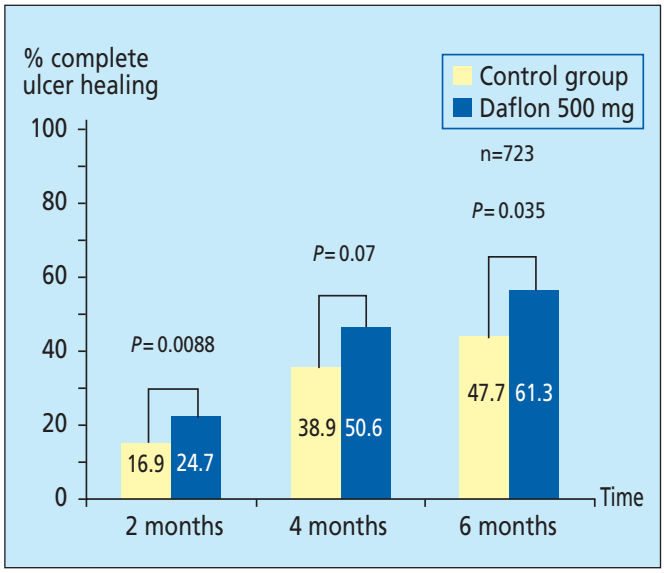

Figure 1. Therapeutic benefit of adding daflon 500 mg to conventional therapy in the treatment of leg ulcers.

accelerates ulcer healing (P=0.003) and results in a greater reduction in ulcer area ($P \leq 0.01$) *(Figure 1)*.

A mode of action at the heart of the disease

Whether the patient complains of the most severe stage of venous leg ulcers, or the initial symptoms and signs of CVI, the pathophysiological mechanisms remain the same throughout the disease. As Prof Nicolaides confirmed in San Diego, the leukocyte adhesion that damages the microcirculation, and is at the heart of venous leg ulcer development, also occurs at the level of the venous wall in early CVI patients. In these patients the subsequent cascade of inflammatory mediators results in the characteristic early symptoms of pain, itching, swelling, lesions in varicose veins, and edema. Daflon 500 mg is the only phlebotropic drug that inhibits leukocyte adhesion and thus the only phlebotropic drug that has demonstrated efficacy at all stages of the disease. Along with this inhibition of leukocyte adhesion, daflon 500 mg also increases venous tone and improves lymphatic drainage, thereby treating all the other aspects of CVI.

In addition, micronization is a high-tech process which reduces daflon 500 mg's mean particle size by 35 µm. Its unique micronized form overcomes the poor gastrointestinal absorption common to all other flavonoids, thereby leading to a faster and better absorption in humans with improved bioavailability. This has been demonstrated in a single-center, double-blind, crossover study in 12 healthy male volunteers who first received a single dose of either radiolabeled daflon 500 mg or radiolabeled nonmicronized diosmin and then, 7 days later, underwent "crossover" for the other drug.[13] The level of absorption was given by the level of urinary radioactivity of either drug. In fact, the level of daflon 500 mg absorption was almost twice that of nonmicronized diosmin, which leads to a more rapid onset of clinical efficacy.

Proof of daflon 500 mg's efficacy on all symptoms and signs of CVI

The efficacy of daflon 500 mg in treating all symptoms and signs of CVI is due to its action on leukocyte adhesion. As with venous leg ulcer development, leukocyte adhesion is central to the development of symptoms and signs, whether in early or late disease. The leukocytes adhere to the venous wall causing endothelial damage, with a subsequent cascade of inflammatory mediators. This then results in the classical CVI symptoms of leg heaviness, itching, pain, painful varicose veins, and general discomfort. In fact, the symptoms that are often seen in patients in the early stages of the disease (C0s to C4) are very debilitating. These symptoms can impact heavily on patient's quality of life.[3]

The evidence for daflon 500 mg's efficacy on early symptoms of CVI comes from the RELIEF study. This was an international, multicenter, prospective, controlled study involving 5052 symptomatic patients (C0s to C4) with or without venous reflux.[3] After a period of 6 months, daflon 500 mg, 2 tablets daily, had significantly reduced symptoms of leg heaviness, leg swelling, and cramps *(Figure 2)*.

In addition to early CVI symptom improvement, daflon 500 mg also demonstrated, in the RELIEF study, an efficacy on the reduction of pain in patients with or without reflux *(Figure 2)*. This improvement in pain was shown to apply for all stages of CVI, from early leg pain to painful varicose veins through to venous leg ulcers.

Final proof of daflon 500 mg's efficacy in treating symptoms of the most severe stage of CVI, namely venous leg ulcers, comes from the meta-analysis. Another aspect of the meta-analysis investigated daflon 500 mg's effect on symptoms associated with venous leg ulcers. A pool of 459 patients with heaviness and pain associated with venous leg ulcers were selected. Primary end points included the percentage of patients without symptoms at 2, 4, and 6 months according to the size/duration of the reference ulcer. daflon 500 mg improved symptoms from 2 months of therapy (and at 4 and 6 months) in ulcers of less than 12 months' duration. This symptom improvement occurred

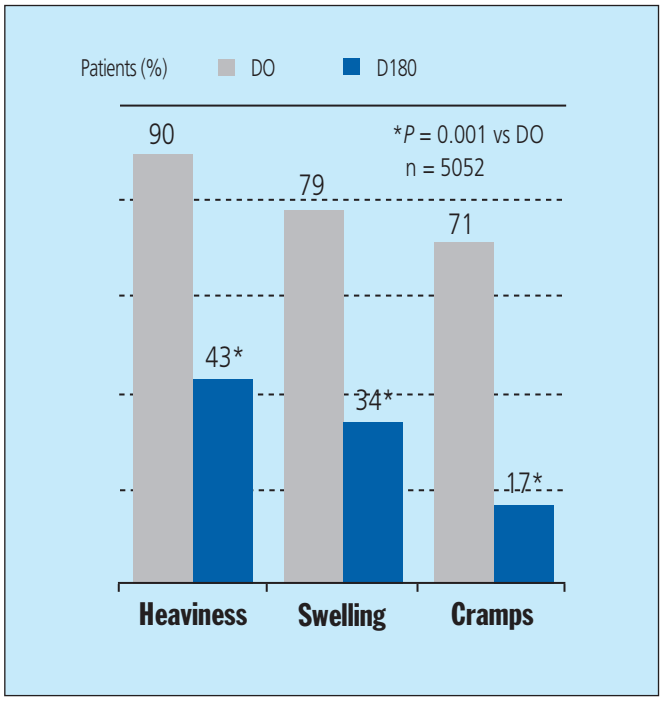

Figure 2. Evolution of symptoms in CVI patients with or without venous reflux during 6-month treatment period of daflon 500 mg.

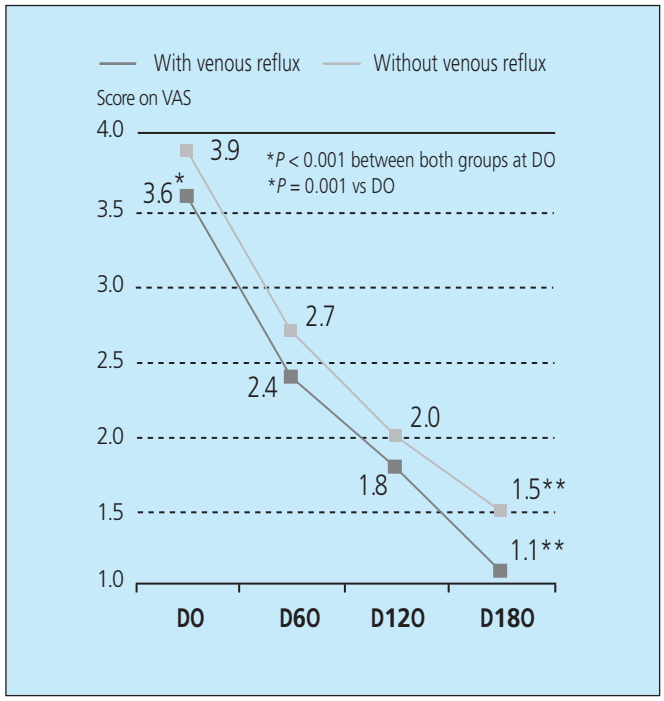

Figure 3. Evolution of pain in CVI patients with or without venous reflux after during 6-month treatment period of daflon 500 mg.

in ulcers <10 cm, >10 cm, and globally (P<0.005).

Along with the well-documented symptoms of CVI, the evolution of edema is a common sign in CVI patients at all stages of disease. Several studies have demonstrated daflon 500 mg's efficacy in reducing leg edema. Using a volumetric technique, Prof Blume showed that, in 20 patients with CVI-associated leg edema, after 6 weeks daflon 500 mg significantly reduces edema by 8% (P <0.001).[14] This improvement in leg edema was confirmed in the RELIEF study using the Leg-O-Meter, a standardized tool enabling the reproducible measurement of ankle circumference at a given level. In patients with or without reflux, daflon 500 mg significantly reduced ankle circumference and thus venous leg edema.[3]

Conclusion

Daflon 500 mg is unique among phlebotropic drugs. The impressive scientific evidence, gathered over many years, for its unique efficacy in venous leg ulcer healing has now been put into perspective by its recognition, in recent years, by the top world experts in the field of phlebology. Moreover, the meta-analysis has provided more incontrovertible proof of its efficacy in venous leg ulcers. The unique comprehensive mode of action of daflon 500 mg with its inhibition of leukocyte adhesion is central to its proven efficacy in CVI in treating the symptoms and signs of early disease (stages C0s to C4) through to those of the most severe complication of venous leg ulcers. Therefore, in any CVI patient who complains of either the very first symptoms or signs (including leg edema) or varicose veins or even venous leg ulcers, daflon 500 mg, 2 tablets daily, is the reference treatment proven to provide immediate and sustained relief to all.

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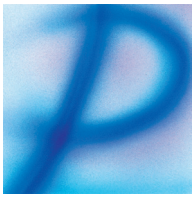

Morphological changes in lymphatic vessels from edema to venous leg ulcer

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INTRODUCTION

Most chronic ulcers of the lower extremity are caused by insufficiency of the deep venous system including the perforating veins. Venous crural ulcer is the last, and a very severe, complication of venous insufficiency. If the deep venous system and the perforating veins are insufficient, then the pressure in the superficial veins is significantly greater. A longer duration of venous hypertension results in increased transudation of plasma to the pericapillary space. As a result, the interstitium is overloaded with fluid, lipids, proteins, and products of cellular degradation. An increased amount of extracellular fluid rich in proteins is transported by the lymphatic vessels. However, their transport capacity is limited. After they are overloaded, they become insufficient, and gradually they become damaged.

From the morphological nomenclature, venous ulcer is a skin defect, presenting as an excavation into the deep layers of the skin and subcutaneous tissues. Some venous ulcerations become secondarily infected. The upper two thirds of the crater are filled with fibrin and granulations, and the lower third is formed by thick tissue, which in long-lasting ulcers develops a very firm consistency. The pathological changes reach to the fascia, but the inflammatory reaction can be present even subfascially. The border of the ulcer is edematous, and the skin around the ulcer is changed by chronic inflammation into lipodermatosclerosis. One of the first anatomical structures that are functionally and later morphologically altered and damaged during the development of venous ulcer are blood vessels. Around the ulcer and in the ulcer itself, pathological changes in the blood vessels and edema of the interstitium have been described.[1] Even though many pathophysiological causes and the resulting alterations which play a role in ulcer development are known, these mechanisms are a constant subject of discussion. There is discussion as to which mechanisms in ulcer development are primary or secondary, and in which order, and to which extent, if all or just some must be present in the development of ulcers. The origin and development of venous hypertension are being investigated with regard to a reduction in the number of microvessels, increased transendothelial and interendothelial permeability to proteins and erythrocytes, impaired endothelial NO synthesis, reduction of tissue fibrinolytic activity, white-cell trapping, the presence of fibrin cuffs and several other possibilities being considered. The list of these has been published in many studies.[1-8, 9]

LYMPHATIC VESSELS - FUNCTIONAL FINDINGS

Lymphatic vessels, which are an integral part of the dermis and subcutaneous tissue in the region of the future venous ulcer, in contrast to blood vessels, are not the focus of attention. The published findings about lymphatic vessels in this region relate to the area around the ulcer and not the ulcer itself. They are mainly of a functional character. Indirect and isotope lymphography have demonstrated lymphovenous anastomoses around the ulcer.[10] In postthrombotic syndrome, isotope lymphography has revealed a decreased or zero transport through the subfascial lymphatic collecting vessel.[11] Using the same method in edema of venous origin, increased as well as decreased flow through the lymphatics has been described.[12-14] Indirect contrast lymphography has shown irregular filling of lymphatics in chronic venous insufficiency,[15] their dilation with extravasation of contrast material, and dermal back flow.[16] In venous insufficiency, fluorescent microlymphography has shown obliteration of part of the superficial lymphatic capillary network of the skin – lymphatic microangiopathy,[17] dilation of lymphatics,[18] and insufficiency of deep lymphatic collectors.[11] In this state, on direct contrast X-ray lymphography, nonhomogenous filling of lymphatic vessels has been demonstrated.[19] With these impaired functions there is release of platelet activating factor of oxygen free radicals which leads to disruption of the muscular pump and valves of the lymphatics.[20,21]

In occasional morphological studies, which considered this problem, destruction of mitochondria in the endothelium of lymphatic vessels was described[22] and a collapse of the lymphatics in the region of the veins altered by varicosities.[23] From the studies discussed it is apparent that in chronic venous insufficiency the lymphatic vessels are functionally altered. Is there morphological change that corresponds to the functional alteration?

MORPHOLOGY OF LYMPHATIC VESSELS OF A VENOUS ULCER AND LIPODERMATOSCLEROTIC ALTERATION OF THE SKIN

On the basis of postmortem studies and tissue biopsies of venous ulcers and lipodermatosclerotically altered skin in 39 humans, using histology, staining, and electron microscopy methods, mild to severe pathological changes were found in the lymphatics.[9]

Venous ulcer

The ulcer was divided into three zones: superficial, intermediate, and deep. The superficial layer reaches from the fibrin of the collagen and inflammatory cell layer to the apex of the blood capillaries. The intermediate layer is rich in vessels and contains blood capillaries, arterioles, postcapillary venules, venules, and granulation tissue. The deep layer of the ulcer is located at the fascia and contains thick collagen fibers and large, partially-to-completely thrombosed veins. In the superficial and intermediate layer, no lymphatics were found. Rarely, in only a small number of ulcers, several lymphatics were found in the transition between the intermediate and deep layers. In the deep layer, in the tissue and around thrombosed veins, occasional lymphatic collectors were found, which were continuations of the lymphatic collectors of the distal parts of the arch and sole of the foot *(Figures 1 and 9)*. Lymphatics were found up to the lipodermatosclerotic border of the ulcer *(Figure 2)*. In the intermediate and deep layer, interstitial edema was present *(Figure 3)*.

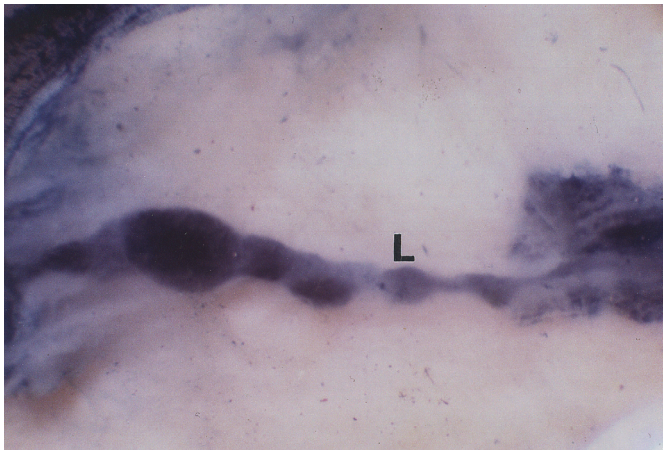

Figure 1. Female 62 years. Lymphatic collector (L) injected with Gerota´s mass traversing the fascia at the base of chronic venous crural ulcer. Cleared specimen, original magnification x 5.

Lipodermatosclerosis of the skin

Lymphatic vessels were dilated at the borders of the ulcer and up to 20 cm from the ulcer and both in the lipodermatosclerotic and normal-looking skin, but with varices *(Figures 4 and 5)*. Electron microscopy showed various degrees of changes in the lymphatics, from normal to severe damage *(Figures 6, 7, and 8)*. In the less severe cases, there is abundant pinocytosis and vacuolization in the endothelial cells. In some lymphatics the endothelium is

atrophic, in others hypertrophic with increased microfilaments. In severely damaged lymphatics the wall is edematous, there are defects of the endothelial lining, and there is apoptosis of the endothelial cells. Collagen fibers protrude into the lumen of the lymphatics through the endothelial defects. Smooth muscle cells in the wall of the lymphatic collectors are vacuolized, in some parts transformed into myofibrocytes, in other parts disintegrated, and their cell cytoplasm is filled with cellular debris. Interendothelial junctions were closed as well as wide open. The collapse of the lymphatic vessel was not observed. In the lipodermatosclerotic skin there were alternating regions of more and less damaged lymphatics.

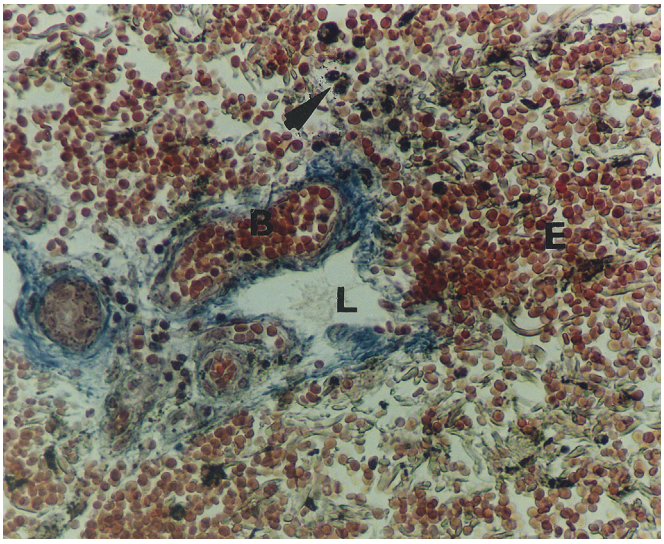

Figure 2. Male 48 years. Lymphatic (L) in the margin of the venous ulcer. B-blood vessel with erythrocytes, E- extravasation of erythrocytes, P-pigment (black dots). Blue trichrome, original. magnification x 90.

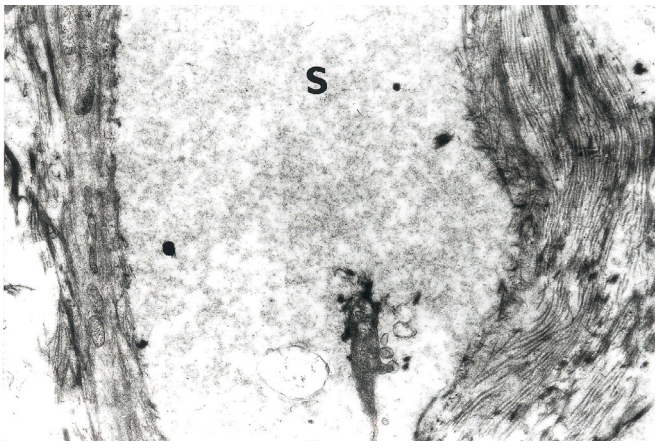

Figure 3. Female 53 years. Dilated interstitial space (S) in crural ulcer between collagen fibers filled with amorphous edema fluid. Electron photomicrograph, original. magnification x 3900.

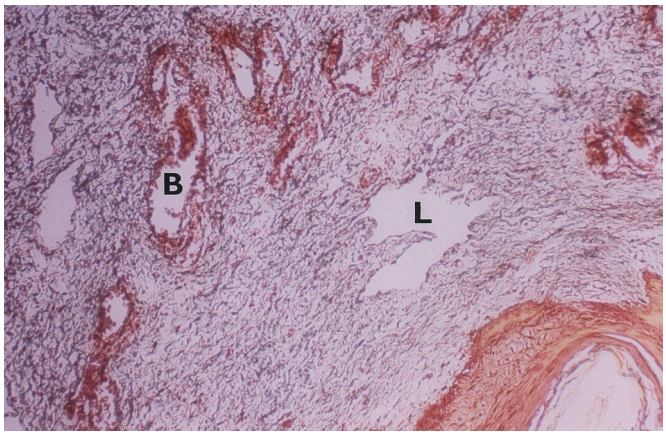

Figure 4. Lipodermatosclerosis. Dilated lymphatics (L) and blood vessels (B). Blue trichrome, original. magnification x 90.

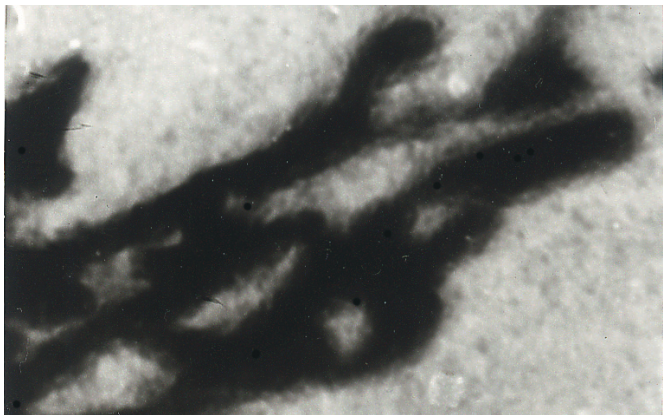

Figure 5. Injected irregular dilated lymph capillaries in lipodermatosclerotic skin. Cleared specimen, original. magnification x 20.

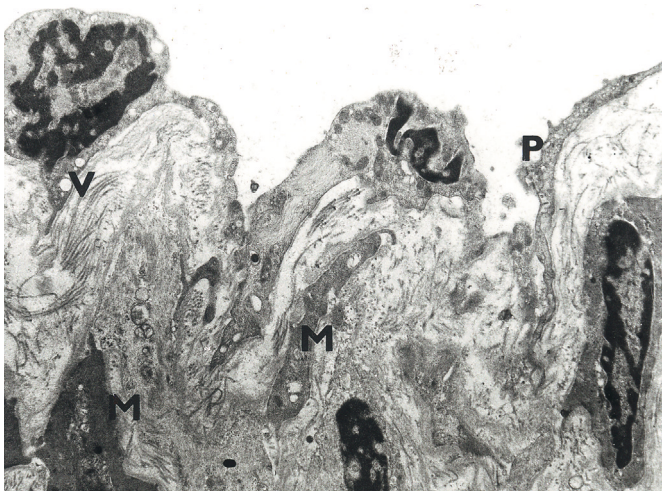

Figure 6. Male 46 years. The wall of the lymphatic vessel in lipodermatosclerotic skin. Thin endothelial lining with pinocytosis (P), vacuoles (V) and deformation of the nuclei. Vacuoles in smooth muscle cells (M). Electron photomicrograph, original. magnification x 5000.

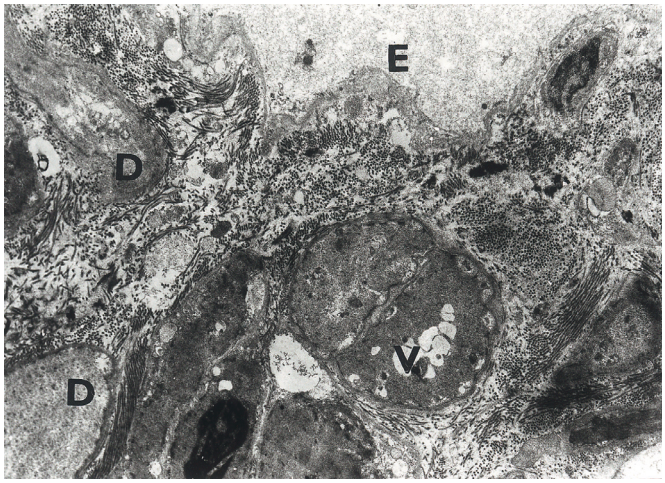

Figure 7. Male 46 years. The wall of the lymphatic vessel at the periphery of the ulcer in lipodermatosclerotic skin. Disintegration of the endothelial cells (E). Smooth muscle cells with vacuoles (V), some of them are destroyed (D). Electron photomicrograph, original. magnification x 4.5000.

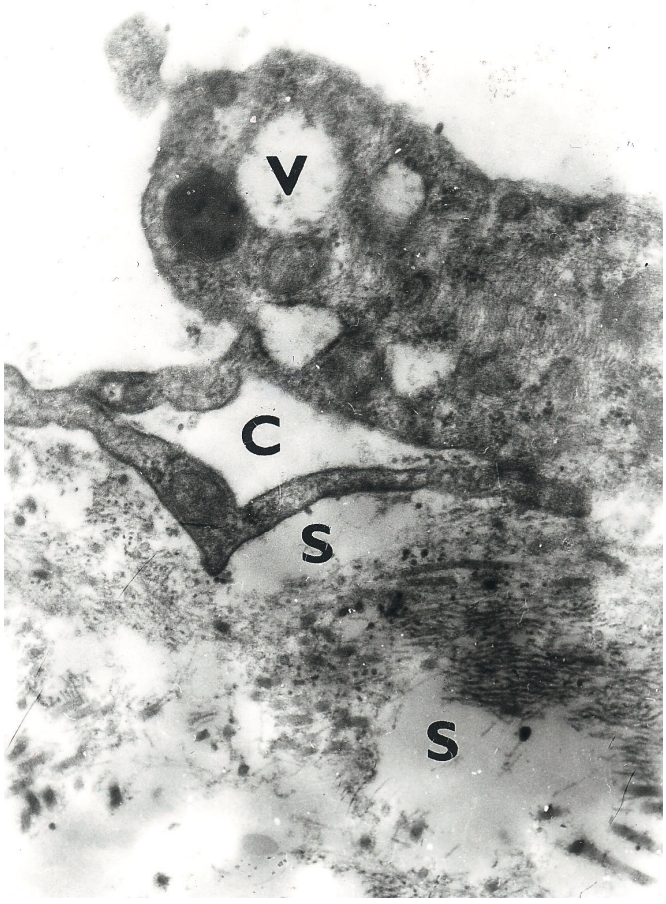

Figure 8. Female 55 years. Lipodermatosclerosis. Lymphatic capillary with large open interendothelial junction in the form channel (C). Subendothelial edema (S). Endothelial cell with large vacuoles (V). Electron photomicrograph original. magnification x 20000.

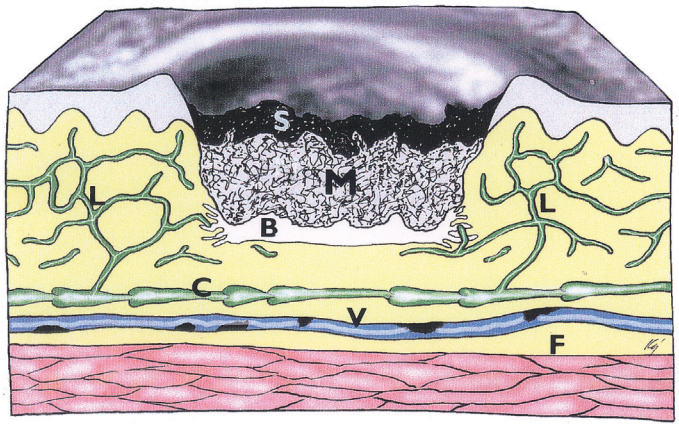

Figure 9 Schema of lymphatic drainage of a venous ulcer. S-superficial part of ulcer-fibrin with apexes of capillary loops. M-middle part of the ulcer -granulation tissue. B- lower part of the ulcer- layer which is formed with the different amount of collagen fibers. In superficial and middle parts lymphatics are absent. Lymphatics were present sporadically in the base of ulcer between its middle and lower part. Lymphatics with various degrees of morphological damage exist in the lipodermatosclerotic periphery and margin of the ulcer (P). Deep lymphatic collector (C) with thrombotic vein (V) on underlying fascia (F).

WHAT CAN BE CONCLUDED FROM THE MORPHOLOGICAL FINDINGS

Several factors play a role in the development of venous ulcer, and these are mentioned at the introduction of this study. From the perspective of pathological anatomy, in the ulcer, blood vessels (veins and blood capillaries) are primarily damaged. Secondarily, there is also morphological alteration of lymphatic vessels. In developed disease, these changes are present side by side. The granulation tissue of the ulcer contains no, or perhaps only a few, sporadic lymphatics. This disrupts the resorption of the increased edematous fluid in the ulcer tissue. Resorption into lymphatic vessels is possible only at the ulcer border where these vessels are present. With regard to the fact that the lymphatic vessels in the lipodermatosclerotically altered skin at the ulcer border and its surroundings are morphologically damaged, the resorption of interstitial fluid is also not adequate *(Figure 9)*.

This is confirmed by the presence of dilated lymphatics, edema surrounding the lymphatics, and widened interendothelial junctions, which, according to the hemodynamic situation, allow for the movement of

edema fluid into the lumen of lymphatics but also back from the lymphatics to the interstitium. Due to the fact that the smooth muscle cells of part of the lymphatic collectors are partially or completely destroyed in long-lasting ulcers, there is disruption of the muscle pump of lymphatics. Considerable pinocytosis, the presence of vacuoles and increased microfilaments in endothelial cells of the lymphatics demonstrates a compensatory reaction of the lymphatics to try and get rid of the increased interstitial fluid. In later phases, there is atrophy of the endothelial cells and their apoptosis. Due to the abundant volume of edematous fluid and pathologically damaged lymphatics, the transport capacity of the lymphatics is decreased. In microscopy samples, most of these vessels are dilated and have significantly irregular contours. The changes in lipodermatosclerosis described here are in different stages of development in a given patient. In areas further from the ulcer, they are less apparent.

Venous ulcer is a chronically open wound, which heals by secondary intention. However, it differs from most secondary healing wounds in which chronic venous insufficiency is not present. An example are wounds healing by secondary intention after surgical procedures.[24] Granulation tissue in both cases is an obstruction for the ingrowth of lymphatic vessels. Nevertheless, in surgical wounds, where there is also edema around the edges, a limited number of lymphatics grow into the edges of the granulation tissue. During wound healing, which is seen as the joining of edges of the defect (contraction of myofibrocytes), the defect is bridged by part of the newly formed lymphatic vessels.[25] In a short time, the blood vessels in the defect connect to the surrounding vascular network. In this way the edema gradually decreases. This is not significant in venous ulcers, due to the almost complete absence of lymphatic vessels in the granulation tissue of the ulcer. Contributing to this is the fact that the granulation tissue of the ulcer is in different stages of development in different areas. There are areas of well-developed granulation tissue, but in some areas there are focal necroses due to the destruction of capillaries (Eliska, Eliskova, unpublished findings). Another difference is that venous insufficiency maintains an increased filtration and permeability of blood capillaries. Thus, venous insufficiency is a continuous source of excess interstitial fluid, which overfills and in the end damages lymphatic vessels. At the same time it maintains long-lasting presence of the granulation tissue. Another disadvantage of venous ulcer is the increase in the tissue at the base of the defect. Here the tissue forms a firm scar that prevents the ingrowth of lymphatics into the ulcer from the undamaged tissues located deep to the ulcer. Insufficiency of lymphatics in the ulcer and damaged lymphatics in lipodermatosclerotic skin are morphological factors that maintain phlebolymphedema and the chronicity of the ulcer, and worsen its healing process. All these morphological changes and damage to the lymphatics, that resulted as a consequence of chronic venous insufficiency, worsen the venous insufficiency itself. By a feedback mechanism, the venous insufficiency negatively affects the lymphatics. This causes a vicious cycle, whose result is visible as improper healing of the venous ulcer *(Table I)*. With respect to these irreversible morphological changes we can expect that even after healing of the ulcer by scarring, the lymphatic vessels of this region remain partially damaged, and thus lead to the recurrence of the ulcer with any smaller load.

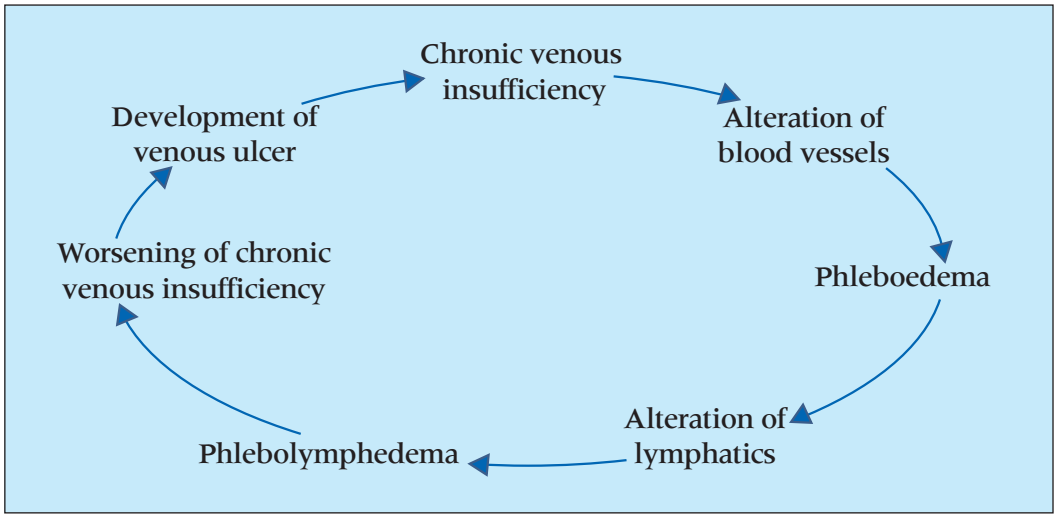

Table 1. Morphology circle in chronic venous insufficiency

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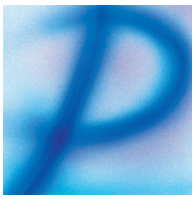

Body image and quality of life in secondary lymphedema of the upper limb

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INTRODUCTION

By definition, the goal of all treatment is to improve the patient's state of health. The quality of life of the patient has an important role to play alongside the objective of cure or remission.

The objectives of contemporary medicine consist not only of prolonging life expectancy, but also lessening the consequences of disease and improving quality of life. Next to physiological parameters, studies of quality of life are invaluable complements to medical assessment in order to evaluate the subjective state of health and its progression.

The repercussions of quality of life in lymphedema result from the actual presence of lymphedema once the dreaded diagnosis is announced, as well as from the therapeutic constraints of its management. They disturb self-perception and modify body image. Secondary lymphedema of the upper limb or "heavy arm" is a major factor among symptoms and sequelae which complicate the life of women after breast cancer and contribute to alteration of quality of life. It is a chronic incapacitating disorder, directly linked to mechanical lymphatic insufficiency induced by treatment-related injury of the lymphatic system, in particular the major collecting lymph vessels of the thorax and axillary lymph nodes.

1. POSTMASTECTOMY LYMPHEDEMA: WOMEN FEEL THEY ARE NOT ENOUGH WARNED

Any woman treated for breast cancer has a risk of developing lymphedema during or after the radio-chemo-surgical treatment necessary to eradicate the tumor. This lymphatic risk may result in the onset of "heavy arm" in almost one woman in two.

Women only rarely notice lymphatic blockage which may take the form of acute lymphedema immediately after surgery and/or radiotherapy. Increase in the size of the arm or hand may disappear almost completely then recur later

and worsen. This change may also persist more or less partially and gradually progress, the woman then living in great hope of recovery.

In the short term, acute edema and lymphocele are in the patient's history adverse lymphatic events which may form the foundations of a "heavy arm."

In the long term, from a few weeks after the treatment of breast cancer to several months (18 months on average), or even a few years, the risk of developing lymphedema may be linked to risk factors which overload lymphatic equilibrium, in particular the woman's lifestyle. It is often noted that women feel that they have not been warned about this risk, nor of the need to modify their lifestyle, and have an attitude of resentment when lymphedema is diagnosed.

The diagnosis confirms that there is imbalance between lymphatic load, ie, the work required from the lymphatic system to eliminate proteins and fluids which cannot recirculate via the capillarovenular system, and the ability of the system to accomplish this work.

This lymphatic stasis leads to protein-rich edema, favorizing the development of connective tissue fibrosis and inflammatory and infectious exacerbations.

2. DIAGNOSIS OF LYMPHEDEMA: AS EARLY AS POSSIBLE

The diagnosis must be made as early as possible to enhance the chances of successful treatment. Analysis of many clinical cases shows that the appearance of fixed edema is preceded by "borderline" states, with intermittent edema appearing during effort and disappearing in a few hours or days. It is essential to act at this stage so as to preserve maximum lymphatic capital and limit the creation of tissue damage which will be reversible only with difficulty.

Women treated for breast cancer often remember small increases in size during or immediately after surgery and radiotherapy, increases in size which reflect the beginning of lymphatic imbalance. Feelings of heaviness, tension, or even painful discomfort are felt, and interfere with their self-perception.

Diagnosis is based upon history and analysis of the characteristics of edema, which usually starts in the arm but also in the hand or forearm. Initially, edema resolves with rest at night, and women generally think that it will always regress until it becomes fixed edema.

3. EVALUATION OF LYMPHEDEMA: CLINICAL AND PSYCHOLOGICAL CRITERIA ARE TO BE ASSESSED

Evaluation must take clinical and psychological factors into account.

Clinical parameters include assessment of size by comparative circumference measurement between the healthy arm and diseased arm, possible infectious exacerbations, ruling out possible shoulder bursitis, changes in the skin, and association with other pathological situations, obesity in particular. Psychological factors include how the patient's self-perception is affected by lymphatic disease and disturbances of body image.

The patient's self-perception must be analyzed, and evaluation of her quality of life and its disturbances will provide additional information.

These evaluation aspects are essential in determining the best management attitude and adapting its intensity.

The treatment of lymphedema is challenging, and is based upon complex decongestive physical therapy:

- General lifestyle attitudes, where the primary objective is to avoid lymphatic risk situations and anything which might increase the workload imposed on the deficient lymphatic system. Living with lymphedema requires a change in habits and obeying new rules. This suppressive lifestyle greatly interferes with the patient's self-perception.

- The goal of physiotherapy is to restore the form and function of the diseased arm. Techniques used are manual lymphatic drainage and nonelastic multilayer bandages. Women have to change their personal and work arrangements because of these treatments.

- Medicines intended to reduce edema.

- Elastic compression-support, in the form of a cuff and/or gauntlet, is aimed at stabilizing the volume of the arm, noting that this treatment method is a further physical and psychological constraint for these women. Justification and explanation are required, and once again education by the practitioner is fundamental. There are criteria for the adaptation of this support: shape, comfort, ease of putting on, psychological acceptability, obtaining stability, climate, lifestyle, etc. The cuff is often poorly accepted and poorly tolerated despite these precautions.

The constraints of treatment are considerable, and are superimposed on the symptoms and signs of the disease, worsening disturbances of body image and quality of life.

Patients are confronted by an esthetic problem, functional problem, and psychological problem as soon as the disease starts.

Lymphedema is a vestige which surprises women "cured" of their cancer. The process from malignant disease to recovery of health by virtue of radio-chemo-surgical treatment is interrupted by the onset of lymphatic disease, which takes on a meaning in everyday life, is known about, can be seen, and is felt. The woman is then once again in a situation of "loss of good health." She has shifted, suddenly or gradually, from the state of health recovered after cure of her breast disease to the beginnings of a lymphatic disease process.

4. LYMPHEDEMA AND MODIFICATION OF BODY IMAGE: ASSESSED WITH THE "MODEL MAN" TEST

Regardless of the patient's ability to adjust, as there was a "before" and "after" cancer, there is a "before" and "after" lymphedema.

At the time of diagnosis of lymphedema, also called "heavy arm" or "elephantiasis," the word about their lymphatic disease and its repercussions on all aspects of life is of incomparable magnitude to women when it is pronounced. The terms "heavy arm" or "elephantiasis"

Subject's last and first names: Date of test:
Age:
1. Grading

	Mark		Mark
1. Head present		27. Hand distinct from fingers and arms	
2. Legs present		28. Arm joints	
3. Arms present		29. Leg joints	
4. Trunk present		30. Proportions of head	
5. Height of trunk greater than width		31. Proportions of arms	
6. Shoulders clearly shown		32. Proportions of legs	
7. Arms and legs attached somewhere to trunk		33. Proportions of feet	
8. Arms and legs attached at proper places to trunk		34. Two dimensions of arms and legs	
9. Neck present		35. Presence of heel	
10. Neck outline		36. Coordination of general outline	
11. Eyes present		37. Coordination of joints	
12. Nose present		38. Coordination of head	
13. Mouth present		39. Coordination of trunk	
14. Nose and mouth shown in 2 dimensions		40. Coordination of arms and legs	
15. Nostrils present		41. Coordination of parts of head	
16. Hair present		42. Ears present	
17. Hair properly located		43. Proportions of ears	
18. Clothes present		44. Details of eyes	
19. Two parts of clothes present		45. Pupils present	
20. Complete drawing of clothes		46. Proportions of eye	
21. Four clearly evident articles of clothing		47. Gaze	
22. Full costume		48. Chin and forehead present	
23. Fingers present		49. Relief of chin	
24. Proper number of fingers		50. Profile	
25. Proper details of fingers		51. Silhouette	
26. Opposition of thumb		Total (Maximum score = 51)	

2. Observation of subject during test
3. Explanation given by subject
4. Psychological diagnosis

Table I. F. Goodenough's "Bonhomme" ("Model Man") tests.

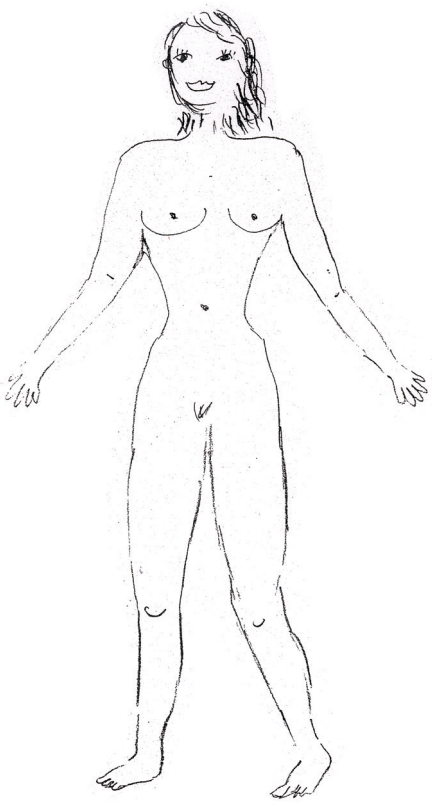
determine from the outset the untoward ugly appearance of this disease process, and this is how women see it and modify their body image.

Body image is an apparently unifying concept. Body image can first be described as a integrating process underlying various skills and learning (eg, identify, name, and correctly localize various parts of one's body). It can also be described as the global configuration which forms the representations, perceptions, feelings or attitudes which individuals construct about their body. Body image is then considered to be a collection of memories, experiences, and attitudes which individuals have accumulated about their own body and which are integrated to varying degrees in a global perception. This is not an image in the strict sense of the term, but rather a collection of representations alluding to the actual physical body but also to the imaginary body.

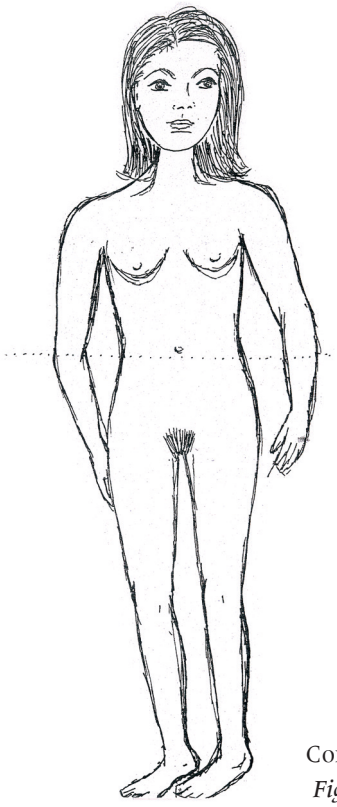
Women suffering from lymphedema have clear changes of body image. These have been analyzed in 270 women, aged between 34 and 69, using the "bonhomme" ("model man") test (*Table I*). Material consists of a black pencil and sheet of unlined white paper. The instruction is to give the woman the sheet showing the phrase: "draw yourself." There must be no remarks nor prompting, the essential being to ensure the greatest freedom possible.

The control group consisted of 30 healthy women. The test response rate was 100%, bearing in mind that 29 women refused to do it at the outset, arguing that that they were bad at drawing, then later accepted.

We sought to evaluate body image in time and space, and to more precisely study the changes, distorsions, and imbalances possibly appearing in these tests when the perfection of the woman with lymphedema is gravely marred. Assessment criteria taken into account included presence of the body, parts of the body and the head and limbs, counted using Goodenough's quantitative score (*Table I*) completed by a qualitative evaluation of the characteristics, traits of lymphatic disease or their omission, disorganization, sexual characteristics and the continuity of the line.



Control 1
Figure 1.



Control 2
Figure 2.

Figures 1 and 2. Feminity is present in drawings by controls . Centering of drawings (on the sheet) is usually good. Sexuel features of the body are well represented.

5. RESULTS OF THE "MODEL MAN" TEST IN 270 WOMEN WITH LYMPHEDEMA

A discontinuous line was present in 89% of patient's drawings, seeming to indicate difficulty producing the outline of the body, either because the woman no longer knew it or because she hesitated to represent it as she knew it, both hypotheses being envisaged (*Figure 4*) .

Centering was good (97%) but it should be noted that 94% of representations were in an immobile position, as if the woman was suspended in time and space and unable to use her body. It was an inert, useless body, impossible to restore to a dynamic state.

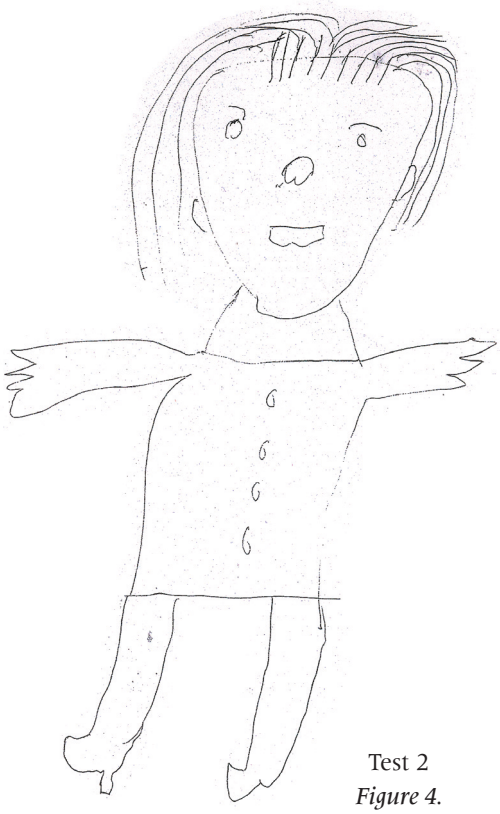
The existing body was 88% represented, but was a body with no features. Its asexual nature was very markedly represented by 81% of drawings where it was seen that whether the body was naked or dressed, it had no visible characteristics of female sexual representations.

However, this absence of signs of femininity should not lead us to think that femininity no longer existed, contrary to what happens with controls (*Figures 1 and 2*) but rather that it played little or less of a determinant role than other features.

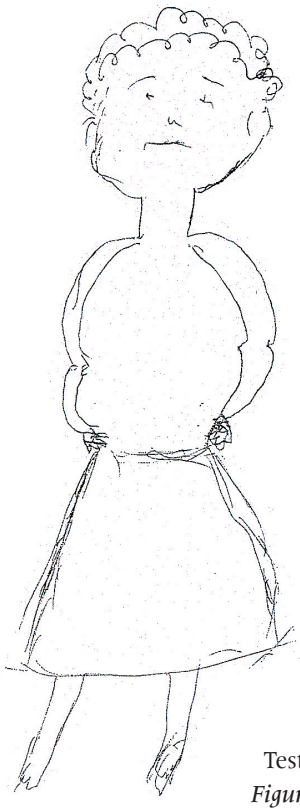
The body was incomplete, and it is interesting to note that incompleteness was marked in 91% by nonrepresentation of lymphedema, either with the limbs being shown as symmetrical (*Figure 3*), or with dissimulation of the diseased hand or arm in a pocket or behind the back (*Figure 5*). It should also be noted that 94% of these women's drawings showed no mark of breast disease and radio-surgical treatments. A final point is that all drawings made women look far younger than the truth, showing young women, with no traits of time or disease, often dressed as little girls (*Figure 3*).

Ninety-four percent of drawings in the control group were drawn with a clear and continuous line and there was a very marked resemblance between the subject and her representation. The body was complete, and sexual characteristics were shown on the naked (*Figures 1 and 2*) or

Test 1
Figure 3.



Test 2
Figure 4.



Test 3
Figure 5.

Figures 3, 4 and 5. A discontinuous may be present (test 2), seeming to indicate difficulty in producing the outline of the body. Representations are mostly in an immobile position, as if women were unable to use their body, and of asexual nature. There is no representation of lymphedema of the arms and moreover the diseased limb may be dissimulated as in test 3.

dressed body. These controls drew themselves smiling in 17 drawings and details of traits of the face and extremities were very delicate.

6. QUALITY OF LIFE: A MULTIDIMENSIONAL CONCEPT BY DEFINITION

Modifications of body image in lymphedema were marked, and showed the painful impact of the disease and its consequences on the life of patients.

The objective of reducing the size of edema should tend to lead to disappearance of the consequences of lymphatic insufficiency but also to revive the self-image of the woman and improve her quality of life.

The term "quality of life" is very widely used and does not take into consideration only physical health. It is a multidimensional concept which covers other areas, chiefly physical, psychological, and social.

Indices of the health status of an individual or group have developed over the past 20 years. These indices provide information for physicians, health care authorities, and the pharmaceutical industry.

In Anglo-saxon countries and France, health care authorities now approve new medicines only insofar as evidence has been provided that they are not associated with any risk of deterioration of quality of life.

Measurement of quality of life has been acknowledged recently as providing a scientific solution to the need to evaluate treatments aimed at contributing not only to lessening symptoms but also restoring a whole series of functions making up quality of life, which may range from mobility to a liking for chatting, doing odd jobs, etc.

Differences in size and circumference between the healthy arm and diseased arm are considered in the case of lymphedema. These criteria are not solely those which the woman takes into consideration and for which she hopes to obtain improvement. It is important to bear in mind the consequences of the disease and the everyday existence of patients.

The concept may seem ambiguous at first sight. It is so vast that everything might be included in it at the extreme limit: environmental factors, family happiness, housing conditions, etc. In order to limit the area covered, quality of life specialists postulate from the outset that they will consider only the consequences of health status on quality of life. The technical expression here is perfectly clear: only quality of life linked to health is dealt with.

Clinicians now use generic scales or specific quality-of-life scales.

The use of generic scales for different diseases and various population types enables comparison between these different diseases and/or populations. However, maladjustment of items in relation to the problem raised may impair sensitivity by inundating pertinent questions in an inert mass.

The specific indices method focusses on areas in which the consequences of the disease are notable, in order to enhance the sensitivity of the tool, ie, to be able to detect slight differences, but which may be clinically significant.

The main stages in the construction of a quality of life index are the creation and selection of a bank of items founded on a qualitative survey of a stratified patient population, as well as on retranscription and classification of verbal quotes, the construction of a "preliminary" questionnaire (format of question, calibration), pretesting and finalization of the preliminary questionnaire, "reduction of items" and the consummation of a quality of life index. Validation evaluates accuracy, precision, and sensitivity of the measurement tool.

The scale is precise if similar results are obtained when measuring the same type of event several times. Precision is determined by looking for the degree of random error. Methods used most widely to assess this are:

Reproducibility of the questionnaire. This is checked by "test-retest" in patients in a stable clinical state. It is presumed that the factor measured in the individual is stable and does not vary between the different measurements made.

Consistency between judges. The consistency test is used above all to assess the agreement between judgements from two different people. A value close to 1 for these tests is a sign of good reliability.

Internal consistency. The various factors making up a given dimension must be homogeneous since they represent the same concept, but with different formulations.

The index is sensitive if it is able to detect minimal changes in a person's quality of life. These changes are clinically pertinent only if they are clinically detectable. According to Guyatt, the score must remain the same in people in a stable clinical state. In contrast, it must vary in those whose state worsens or improves.

Three approaches have been used up to now to measure quality of life: batteries of indices, psychometric scales, and usefulness functions. Clearly, none is a panacea. It is also helpful to undertake an exploratory study in patients with

a given disease in order to ensure that the problems accompanying it can actually be represented in existing "general" tools. A specific index must be created if that is not the case.

7. QUALITY OF LIFE IN LYMPHEDEMA: A SPECIFIC SCALE IS NECESSARY

Construction of a specific scale for secondary lymphedema of the upper limb proved necessary.

Methods used to construct such a tool were based upon statements from patients concerned and/or interviews of experts. Semi-structured discussion with a panel of women with lymphedema led to the establishment of a bank of 1106 verbal quotes culminating in a list of 906 questions. Patients' verbal quotes identified a number of physical, psychological, or social complaints, while an overall feeling of poor health emerged.

The functional effects of lymphedema on locomotor ability elude the usual norms of generic indices. Difficulty walking is due less to stiffness or pain than to heaviness of the arm.

"Walking with the arm swinging is heavy on the shoulder."

"When I walk with my arm hanging down, it obviously swells. I feel that everything is slipping down."

Very specific limitations emerge concerning very precise gestures: "holding the arm in the air, leaning on the arm, bending it, moving the fingers" are all difficult movements. Basic acts, such as "grasping and holding an object, opening faucets, making precise movements, opening a car or train door handle" are severely impaired. Sleep is difficult for very precise reasons. It is no longer possible to find a comfortable position and it is often necessary to give up sleeping on the side of the diseased arm and learn how to sleep on the other. If the arm "gets stuck" inadvertently, it wakes the patient up.

Restrictions in the everyday activities are all obstacles to carrying out basic tasks and can hence be used to quantify the person's activity much more usefully than symptoms or behavior. Many gestures involved in personal care are more difficult to perform. Washing is laborious because of the need to keep the arm in extension or lean on it. *"Getting out of the bath is dreadful." "I no longer brush my hair." "Dressing, hooking your bra, putting on a coat, putting a chain around the neck"* are all difficult.

There are the usual psychological repercussions in terms of anxiety and depression. In contrast, lymphedema is accompanied by quite specific mental suffering caused by its inherent esthetic problems. Patients worry constantly, which takes on various guises:

The constant fear of an injury: *"I'm afraid of catching, pricking, or scratching myself." "I used to like to travel but now I'm afraid."*

The dread of lymphangitis and worsening of it : *"I constantly think that it might get bigger." "My only fear is paralysis."*

The feeling of being a millstone, of being a burden to everybody: *"I don't want to be a nuisance, someone to be pitied."*

Esthetic suffering is linked to what others see: *"You feel really pathetic when you go to buy clothes. The salesperson, who is behind you in the fitting cubicle- its terrible."*

There is finally loss of self-esteem. You can no longer look at yourself in a mirror: *"I haven't seen myself for a year. I look in a very small face mirror to brush my teeth."*

Social consequences are the effects of lymphedema on all the potential activities of the people questioned based upon their role in society. This covers, for example, work in active individuals, housework in women staying at home, and hobbies or pastimes in the active or inactive.

Handling heavy objects at work (packages, books, pieces of equipment) is difficult. Writing and computer work are tiring. All these difficulties require a redistribution of tasks. Patients very often request a change of job assignment: *"I can't play the action woman any longer. I very much know what I need and what I don't need, it's quite certain: a quieter life and fewer responsibilities."*

Following the elimination of redundant or poorly expressed statements, a first 73-item questionnaire was administered to 154 patients. Factorial analysis identified the main dimensions of the disorder and 55 superfluous questions were discarded. The second questionnaire consisted of 28 items and was tested on 301 patients. This was followed by a further analysis to ensure the stability of the factorial structure, which led to the creation of a third questionnaire consisting of 27 items.

8. CONCLUSION

Clinicians have access to a measurement tool enabling them not only to evaluate lymphedema and its pathological effects, but also to evaluate the impact of various treatments. The quality-of-life scale in secondary lymphedema of the upper limb after breast cancer is a technological advance for the use of scientists and benefit of patients.

The practitioner chooses and modifies treatments, taking into account the variability of patients' reactions, clinical results obtained, and implications on quality of life due to the disease and its management. The size of the arm alone cannot account for the complexity and severity of the repercussions of lymphedema on the life of patients, especially in the functional and psychological areas. Study of changes in the various components of quality of life can help the clinician to quantify the results of treatment and adjust the management and monitoring of women with lymphedema.

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FURTHER READING

Alliot F, Cluzan RV, Sthevenin Ph, Bleton JP. The body image in lymphoedema; remarks. In XVI World Congress of International Union of Angiology. Paris 1992.

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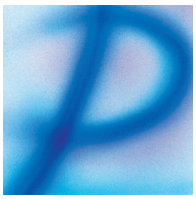

Congress and conference calendar

INTERNATIONAL UNION OF PHLEBOLOGY (IUP) NORTH AMERICAN CHAPTER

This congress will be held in San Diego (USA) from August 27 to 31, 2003.

• *For further information, please contact:*

American College of Phlebology
100 Webster Street, Suite 101
Oakland, Ca 94607 - 3724, USA
Tel: + 1 510/834-6500

XIXth INTERNATIONAL CONGRESS OF LYMPHOLOGY

This congress will be held in Freiburg (Germany) from September 1 to 6, 2003.

• *For further information, please contact:*

President: Dr E. Földi

Scientific organizing secretariat:
P. Martin
Clinic for Lymphology
Roesslehofweg 2-6
79856 Hinterzarten, Germany

Tel: + 49 7652 12 40
Fax: + 49 7652 12 41 16
E-mail: foeldi@foeldiklinik.de

Organizing Secretariat:
INTERCONGRESS GmbH
Tel: + 49 761 52 12 40
Fax: + 49 761 6 96 99 11
E-mail: isl@intercongress.de
Website: www. intercongress

XXVIIth ANNUAL MEETING OF EUROPEAN SOCIETY FOR VASCULAR SURGERY

This congress will be held in Dublin (Ireland) from September 4 to 11, 2003.

• *For further information, please contact:*

President: Prof Michael Horrocks

School of Postgraduate Medicine
University of Bath
Clavertown Down
Bath BA2 7AY, UK

Tel: + 44 1225 323 770
Fax: + 44 1225 323 669
E-mail: S.Needhham@bath.ac.uk

VIIIth NATIONAL CONFERENCE OF COLLOPROCTOLOGY

This congress will be held in Varna (Bulgaria) from September 25 to 27, 2003.

• *For further information, please contact:*

President: Prof Dr Temelko Temelkov

Organisational committee: Dr Ignatov

Tel: + 359 52 30 28 63
Fax: + 359 52 30 28 69

XXIIIrd ASEAN ORTHOPAEDIC ASSOCIATION CONGRESS

This congress will be held in Kota Kinabalu, Sabah (Malaysia) from October 2 to 5, 2003.

• *For further information, please contact:*

Secretariat: No 19, Jalan Folly Barat
50480, Kuala Lumpur, Malaysia

Tel: + 603 2093 0100 / 2093 0200
Fax: + 603 2093 0900

President: Assoc Prof Sharaf Ibrahim (Organizing Chirman)

VIIth NATIONAL CONFERENCE OF ANGIOLOGY AND VASCULAR SURGERY

This congress will be held in Zlatni (Bulgaria) from October 3 to 5, 2003.

• *For further information, please contact:*

President: Prof Todor Zachariev

Secretary: Dr Stankev

Tel: + 359 2 920 22 56 (484,415)
Fax: + 359 2 954 90 57
E-mail: tzah@intech.bg ; mstang@yahoo.com

VASCULAR MEDICINE 2003 XVth EUROPEAN CHAPTER CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY & NATIONAL MEETING OF THE FRENCH SOCIETIES OF VASCULAR MEDICINE

This congress will be held in Toulouse (France) from October 8 to 10, 2003.

• *For further information, please contact:*

President: Prof H. Boccalon

CHU Rangueil
Service de Médecine Vasculaire
1, avenue Jean Poulhès
31403 Toulouse Cedex 4, France

Tel: + 33 5 61 32 24 38
Fax: + 33 5 61 32 26 34
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EUROPA ORGANISATION

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31015 Toulouse Cedex 6, France

Tel: + 33 5 34 45 26 45
Fax: + 33 5 34 45 26 46/ 47
E-mail: europa@europa-organisation.com

THE MANAGEMENT OF REFLUX AND OBSTRUCTION OF THE DEEP VENOUS SYSTEM

This congress will be held in London (UK) on October 10, 2003.

• *For further information, please contact:*

Organizer: Mr G. Geroulakos
Jo O'Neill
Academic Department
Royal Society of Medicine
1 Wimpole Street
London W1G 0AE, UK

Tel: + 44 (0) 20 7290 3918
Fax: + 44 (0) 20 7290 2989
E-mail: angiology@rsm.ac.uk
Internet: www.rsm.ac.uk/angiology

ANNUAL MEETING OF AOD WORKING GROUP OPERATIV DERMATOLOGY (Arbeitsgruppe operativer Dermatologie)

This congress will be held in Wels (Austria) from October 10 to 12, 2003.

• *For further information, please contact:*

Prim Dr Mishcer, OA Dr Saxinger
Congress Management: MFC Masi Fuchs Congress

Tel: + 43 1 602 25 48
Fax: + 43 1 602 25 48
E-mail: congress@telering.at

VIIth NATIONAL CONGRESS OF THE ITALIAN COLLEGE OF LYMPHOLOGY "PHLEBOLYMPHOLOGY 2003"

This congress will be held in Udine (Italy) from October 12 to 14, 2003.

• *For further information, please contact:*

Dr Intini
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Tel: + 39 0432 55 95 59
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President: Pr of Dino De Anna
Casa di Cura S. Maria Maddalena
Via Gorizia N.2
45030 Occhiobello (Gorizia), Italy

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VSICON 2003

This congress will be held in Goa (India) from October 16 to 19, 2003.

• *For further information, please contact:*

President: Organising Chairman – Dr Anand Somaya
Organising Secretary: Dr Pankaj Patel
Tel: + 91 22 2 455 5320
Fax: + 91 22 444 9536
E-mail: vsibeachcon2003@hotmail.com
Internet: www.vsibeach2003.com

XIth UNITED EUROPEAN GASTROENTEROLOGY FEDERATION (UEGF)

This congress will be held in Madrid (Spain) from November 1 to 5, 2003.

CONGRESSO NAZIONALE GIUV

This congress will be held in Montecatini (Italy) from November 6 to 9, 2003.

• *For further information, please contact:*

Dr D. Righi
Chirurgica Vascolare
Policlinico di Careggi
Firenze, Italy
Tel: + 39 055 42 77 574
President: Dr Antignani
Istituto S. Camillo
Divisione di Angiologia
Roma, Italy

XXVth NATIONAL CONGRESS OF ITALIAN SOCIETY FOR ANGIOLOGY AND VASCULAR MEDICINE (SIAPAV)

This congress will be held in Rome (Italy) from November 23 to 27, 2003.

• *For further information, please contact:*

GC Congressi
Via P. Borsieri, 12 – 00195 Roma
Tel: + 39 06-37.29.466
Fax: + 39 06-37.35.23.37
E-mail: md2535@mclink.it
President: Prof C. Allegra
Ospedale San Giovanni – Reparto di Angiologia - Roma
E-mail: c.allegra@pronet.it

XXIst NATIONAL CONGRESS OF ITALIAN SOCIETY FOR MICROCIRCULATORY STUDIES

This congress will be held in Rome (Italy) from November 23 to 27, 2003.

• *For further information, please contact:*

President: Prof Sandro Forconi
Organizing Secretariat: Dr Mancini
Tel: + 39 06 37 00541-37 29 466
Fax: + 39 06 37 35 23 37
E-mail: md2535@mclink.it

VASCULAR SURGERY SOCIETY OF GREAT BRITAIN & IRELAND

This congress will be held in Glasgow (UK) from November 26 to 28, 2003.

• *For further information, please contact:*

Administrator: Miss J Robey
35/43 Lincoln's Inn, UK
Tel: + 44 20 797 30 306

1er ENCUENTRO INTERNACIONAL SOBRE INSUFICIENCIA VENOSA CRONICA SUBDIAFRAGMATICA, ABDOMINO PELVICA Y DE MIEMBROS INFERIORES

This congress will be held in Madrid (Spain) from November 27 to 28, 2003.

• *For further information, please contact:*

Dr J Leal-Monedero / Dr S Zubicoa Ezpeleta
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La Masó, 38
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APICON 2004 – 59th JOINT ANNUAL CONFERENCE OF ASSOCIATION OF PHYSICIANS OF INDIA

This congress will be held in Hyderabad (India) from January 18 to 22, 2004.

• *For further information, please contact:*

Organizing Secretary: Prof BK Sahay
Tel: + 99 040 23 41 44 35
E-mail: apicon2004@rediffmail.com

XXIIth WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY

This congress will be held in Rome (Italy) from May 22 to 26, 2004.

• *For further information, please contact:*

Scientific Secretariat
Via Sardegna, 76
90144 Palermo, Italy
Tel: + 39 91 511 375

XIIth UNITED EUROPEAN GASTROENTEROLOGY FEDERATION (UEGF)

This congress will be held in Madrid (Spain) from Septembre 25 to 30, 2004

EUROPEAN SOCIETY OF SURGERY – VIIIth ANNUAL MEETING

This congress will be held in St Julian's (Malta) in November 2004

• *For further information, please contact:*

President: Prof L. Cutajar
Chairman, Organising Committee, ESS Meeting
Department of Surgery, The Medical School
G'Mangia, Malta

INTERNATIONAL UNION OF PHLEBOLOGY (UIP) XVth WORLD CONGRESS

This congress will be held in Brazil (Rio de Janeiro) from October 2nd to 7th, 2005.

• *For further information, please contact:*

President: Angelo Scuderi, MD
Universita di Ferrara – Chirurgia Vascolare
Rio UIP 2005
Rue Sancta Clara, 494
Sorocaba - SP - 18035 - 421
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A leading company in the field of phlebolymphology,
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