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# LYMPHOLOGY IN THE SECOND MILLENNIUM*

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On the threshold of the third millennium, looking back to the second, I shall focus on lymphedema, a disorder which is the most common, and, accordingly, the most important problem in lymphology.

It seems certain that in ancient times, the Greek word "elephantiasis" stood for the tuberous form of lepra and that it referred to the elephant. Aretaes wrote in 50 AD: "Elephanti morbo cum belua elephanti multa sunt communis, quoad speciem et magnitudinem." ("The disease elephantiasis has much in common with the monster elephant in regards to species and largeness.")

The Arabian physicians were the first to clearly differentiate between the elephantiastic form of lepra which they termed Judam and those clinical pictures which represented the final stage of lymphedema, both in its pure, as well as in its combination forms: these they called elephantiasis.

At the turn of the first millennium Avicenna, the famed Arabian physician, who lived between 980 and 1037, in his book , "De elephantiasi seu tumore pedum" (of elephantiasis, and swelling of the feet) provided an excellent description of sporadic lymphedema which arose in the final stages of chronic venous insufficiency (CVI).

In the 16th century, the Italian Prosper Alpino, who was the physician for the Venetian ambassador to Egypt, encountered many patients with what we now call "tropical elephantiasis" (formerly the term "elephantiasis arabum" had been used). His ideas concerning etiology, published in 1541, are worth quoting: "Vagetur ... Elephantiasis ... qua correpti pedes multis magnis duris tumoribus tumidos magnos atque deformes habent, pedibus elephantium maxime similis quibus tamen ager nihil doloris sentit sed ad ambulandum ineptus redditur ... Ex malo victu . . .ex piscium Nili ac ... lacuum stagnantium semiputidarumque aquarum multam pitutiam crassam lentamque gignunt, quae ad pedes defluxa illos scirrhosos oedematososque tumores pedibus creat". ("Elephantiasis is a widespread disease ... those who suffer from it have huge, swollen, disfigured legs, caused by many big hard tumors: they look very much like those of an elephant. Nevertheless the sick person does not notice any pain, but becomes unable to walk. Out of bad food, e.g., of fish coming from the Nile and from stagnant putrid lakes, a lot of coarse and sticky mucus develops which flows down to the legs creating these scirrhous and edematous tumors.")

In his epic text *(Fig. 1)*, published in 1787, Mascagni describes the role of the lymphatic system in the formation of edema: "Primam speciem vocat, ubi glandulae obstructae sunt. Secundam speciem ... a dilatatis vasis absorbentibus derivat, ubi valvulae regressum non impediumt." ("Those edemas which are caused by the obstruction of the lymph nodes belong to the first group, those which are due to such a dilatation of

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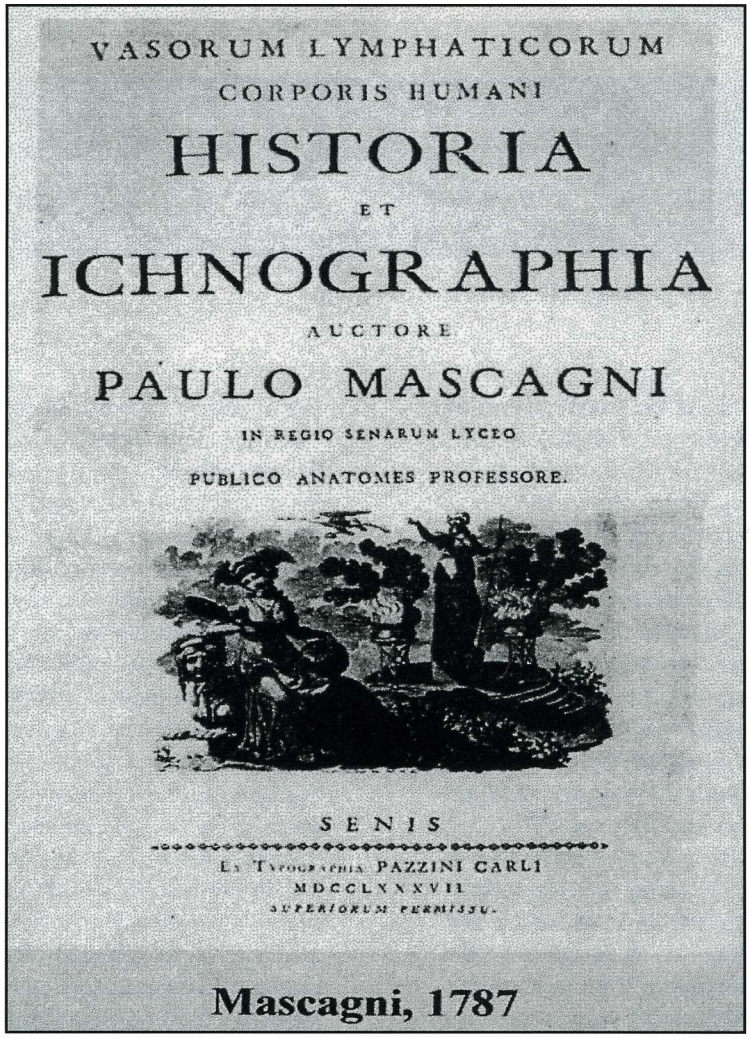



*1. Epic text by Paulo Mascagni on the lymphatic vessels.*

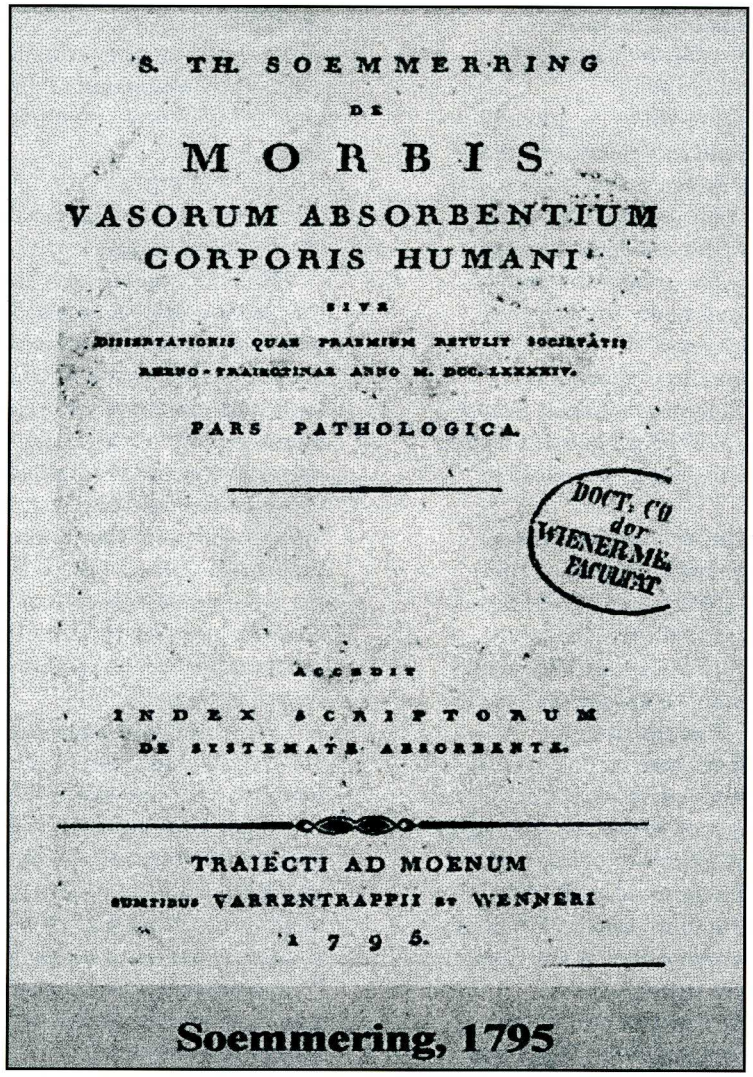
the lymphatics which makes the valves inadequate to prevent the retrograde flow of lymph belong to the second group.")

Quite remarkable descriptions can be found in the book of Soemmering *(Fig. 2)*, written in Latin, published in 1795. I have translated the most interesting ones:

"Quidquid lymphae motum ... impedit, potest oedemati occasionem dare." ("Everything which impedes lymph flow can result in edema")

"Oedemata explicantur a vasorum absorbentium potius quam a venarum compressione." ("Rather than by the compression of veins the edemas can be explained by that of the lymphatics.")

"In femina robusta ... vasa sorbentia eiusdem cruris adeo varicosa vidi, ut oedematis pedis speciem praeberent ... cuum impetu lympham prosilientem vidi e vase tali varicoso, vel acu vel lanceolo in hac femina aperto." ("...On the shank of an adult woman I have seen such extremely varicose lymphatics that they have caused a picture of


S. TH. SOEMMERRING

DE

MORBIS

VASORUM ABSORBENTIUM

CORPORIS HUMANI

SIVE

DISSERTATIONIS QUAM PRAEMIUM RETULIT SOCIETATIS

HARLEMO-TRAIECTINAE ANNO M. DCC. LXXXXIV.

PARS PATHOLOGICA.

DOCT. CO dor WIENER ME FACULTET

ACCEDIT

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DE SYSTEMATE ABSORBENTE.

TRAIECTI AD MOENUM

SUMTIBUS VARRENTRAPPII et WENNERI

1795.

Soemmering, 1795

*2. Latin text by S.Th. Soemmerring on the "absorbing vessels" [lymphatics].*

the edema of the leg ... in this woman after having opened the lymph vessel either by a needle or by a lancet, lymph has poured with great force.")

"Vulnerato enim vasorum sorbentium majori trunco quodam vulnere oedema oboritur ab obstructione viae, per quam lymphae in sanguinem redeundum est. Non raro id post exstirpationem glandularum axillarum accidere solet. Oedema ... tali modo obortum tamdiu durat: donec vasa sorbentia laterali eo usque extendantur, ut eorum amplitudo sufficiat ad lymphae insolitam quantitatem transmittendam." ("By the occlusion of the pathway through which lymph flows into the blood, by wounds which effect the lymphatics edema appears. Not rarely after the extirpation of the axillary lymph nodes. An edema which arises in this way lasts for a very long time, for as long as

collateral lymph network has become established which is able to transmit the unusual quantity of lymph.")

"Oedemata pedum videre in gravidis, a pressione uteri gravidi in vasa absorbentia glandulasque absorbentes pelvis, quae partu edito sanantur." ("One sees leg edemas of pregnant women which are caused by the pressure exerted by the pregnant womb on the lymph vessels and nodes in the pelvis which heal after delivery.")

"Calculum ... in Ducto thoracico ... inventum pro causa hydropis habuit Scherb (1729)." ("Scherb [1729] has regarded a stone found in the thoracic duct as the cause of edema.")

"Post usum cantharidum fere semper vasa absorbentia obstructa invenisse vult - Mascagni (1789)." ("Mascagni [1789] has found almost always that after the use of cantharidin the lymphatics were occluded").

"Concludo, quum verum oedema pedis natum viderim a vulnerato vasculo absorbente in malleolo interno decurrente." ("I conclude with the remark that I have seen a real edema of the foot which has developed as a consequence of an injury of the lymph vessel situated in the internal malleolus.")

"...musculum motu promoveri lymphae fluxum ..." (..."The movement of the muscles promotes the flow of lymph...")

Hendy, in 1796, makes a distinction between elephantiasis caused by lepra and that caused by diseases of the lymph nodes. In his book "The Disease of Lymph Glands in Barbados" he writes: ,"The lymph nodes are enlarged and filled by a gelatinous fluid. This causes a stagnation of lymph in the tissues. The lymphatics in the foot dilate; one can easily insert a quill and if one injects mercury, mercury droplets pass through their wall. Lymphorrhoea is present. The disease is caused by altered climatic conditions due to the foolish routing out of the forests".

Alard, in his book entitled "Histoire D'une Maladie Particulaire Au Svstème Lymphatigue," published in 1806 in Paris, stated that the underlying pathology of elephantiasis tropica (arabum) is lymphangitis, caused by colds caught during chilly nights, by sleeping next to open windows, by repeated change of weather, and by cool winds.

The Englishman Rust, too, in 1832, described tropical elephantiasis as a disease of the lymph vessels.

It is remarkable how already, in 1844, the German Herbst recognized the role of intraluminal valves and how much he knew about lymphodynamics. One reads in his book, that the valves prevent retrograde injections into a lymphatic, that there are no valves in the initial lymphatics, that the valves in the thoracic duct, near to its inosculation with the venous angle, serve to prevent backflow of blood into the duct, that the lymphatics have a marked ability to contract and that the speed of lymph flow of the lymph correlates positively with the degree of their filling!

The renowned pathologist Virchow, in 1854, called attention to the occlusion of lymph vessels and nodes by inflammatory processes, by lymphostasis, by proliferating cells and by perinodular infiltrations, causing "lymphatic edema." He regarded elephantiasis as an inflammatory and exudative process, the underlying pathology of which "corresponds to the connective tissue proliferation and shrinking of the lungs in pulmonary cirrhosis."

A milestone concerning the etiology of tropical elephantiasis was the discovery of Wucherer in 1866, who found the parasite filaria in chylous urine and that of Manson in 1875 who discovered filaria in chylocele, in lymphorrhoea and in chylous diarrhea.

In their book entitled "The Elephantiastic Forms," published in 1885, Esmarch and Kuhlenkampff have accurately written "The analysis of the data shows that elephantiasis is due to alterations of the lymph vascular system." They defined it as a chronic disease, triggered by disturbances of lymph flow and of the flow in tissue channels; it is accompanied and often triggered by acute

inflammations. It results in an increase of the mass of the cutis and mainly of the subcutis. They were well aware of the fact that in some cases of elephantiasis of the female genitalia, papillomatous, tumor-like structures develop, similar to condylomata acuminata. Concerning the etiopathogenesis of sporadic elephantiasis appearing sometimes after birth, these authors attributed malformations of the lymph vessels, lymphangiectasia, defective valves, partial occlusion, abnormal course and abnormal entry into the venous angle as responsible causations. They also regarded the aim of treatment was to restore the circulation of stagnating tissue fluid and abolish inflammatory attacks. They employed, what we call today, "complex decongestive physiotherapy (CDP)," a combination of massage, of compression, of skin care and of remedial exercises. They stressed that the treatment of any accompanying disease is mandatory. According to their experience the swelling disappears if scar-like sclerosis has not yet developed. But "if the compliance of the patient is inadequate, if he does not practice caution, if he is not willing to accept a chronic treatment of his chronic disease, improvement will only be transitory ... The results of the physical therapy of lymphedema depend on the manner in which it is applied. Massage, for example, necessitates not only great persistence and skill but also such expenditure of time which not every physician can allow himself. Due to the fact that this conservative treatment does not result in healing of elephantiasis, it is small wonder, that all along, surgeons have looked for more effective methods."

Carnochan reported in 1851 that he achieved great success in one patient by ligating the femoral artery ... Instead of the femoral artery, Hueter, in 1886, chose the external iliac artery for ligation ... It is impossible to find out, whether the decongestion, which one occasionally observes after these operations, is due to the ligature of the artery or whether it is pure coincidence or is perhaps due to the fact that during several postoperative days, huge amounts of edema fluid discharge from the wound."

Esmarch and Kuhlenkampff also refer to Syme, who in a paper, published in 1866 in the Edinburgh Medical Journal maintained that this procedure lacks any sound surgical principle. According to an article of Fayrer, published in 1879 in "The Lancet", the ligatures which he has performed had a temporary effect only and that this effect did not exceed that which one can achieve by bed rest, by the elevation of the limb and by compression.

The judgment of Wernher in 1875 concerning arterial ligations was very negative. From 32 patients one year after the operation an improvement was found only two times, amputation was necessary two times, severe bleedings occurred in three patients and three patients died immediately after the operation.

In the 18th century, Hendy had introduced another surgical method-scarification. It was practiced in the first half of the 19th century by Blasius in Germany and by Lisfranc in France and we have seen it — it seems incredible but it is true — in one patient, operated by a German surgeon as late as 1980.

The famous dermatologist Kaposi also devoted his attention to lymphedema. He wrote in 1878: "The diffuse hypertrophy of the connective tissues of the skin has to be ascribed to the piling up of interstitial tissue fluid." He accepted Virchow's view that elephantiasis was due to "lymphatic edema" with an inflammatory character. He gave an excellent description of all the signs and symptoms of lymphedema including Stemmer's sign! He had a clear view concerning the difference between protein poor and protein rich edemas. He wrote: "Serous edemas, e.g., those which are triggered by congestion of blood in the veins and those which are caused by renal diseases never lead to a hypertrophy of the connective tissue, only inflammatory edemas."

For treatment Kaposi recommended, as did Esmarch and Kuhlenkampff, complex decongestive physiotherapy. He, too, condemned the ligature of arteries. He wrote: "With the exception of those, who died because of gangrene and septicemia, in those, who survived the operation, the reduction of edema did not exceed the extent which is brought about by the bed rest for several weeks duration which is required post-operatively."

Winiwarter published in 1892 a book still worth studying about elephantiasis. According to him: "elephantiasis often starts with an acute inflammation to become a chronic inflammatory process characterized by disturbance of lymph and tissue fluid flow. As a consequence of the proliferation of connective tissue, the skin and the subcutis thicken and the volume of the affected limbs increases."

Winiwarter described two forms of lymphedema, a pure, uncomplicated/form and a combined form. He explained the pure form derives from obliteration of lymph vessels by malignancies, lymphothrombosis and from "indurated" lymph nodes, whereas the combined forms includes venous outflow hindrances such as compression of deep veins, varicosities and phlebitis. Like Kaposi, he called attention to the fact, that lymphedema fluid is rich in proteins; after its removal it coagulates.

Winiwarter also provided a detailed description of pathologic changes: "The lymphatics are dilated, their walls have become either thick or, to the contrary, thin. Excrescence of the endothelial cells and lymphothrombosis cause obliteration of the lumen of some lymphatics."

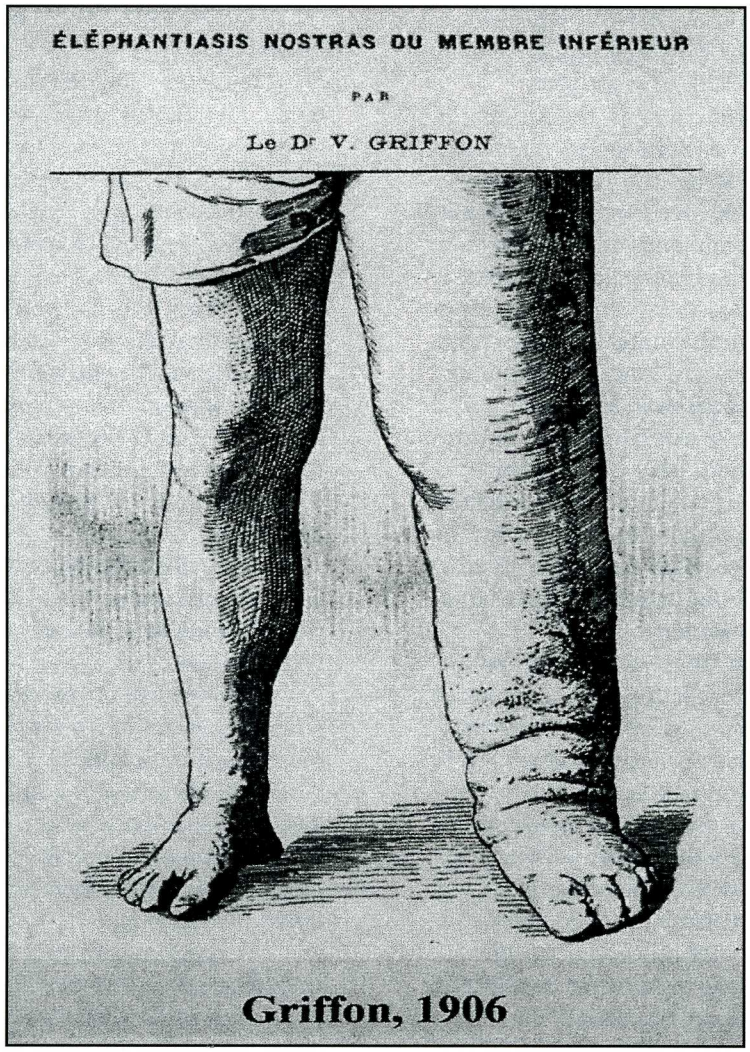
For treatment, he recommended CDP. He stressed, that the results of the treatment "depend greatly on the personal intervention and the experience of the physician. Therefore, the results of the same method achieved by different physicians, differs greatly." According to his experience "the results of the conservative treatment are quite satisfactory, but the patients have to comply. The effect is poor, if the patient has to work hard, if he does not have time, money and brains to take care of himself long enough to avoid those harmful factors which trigger relapses."

It is noteworthy that Winiwarter was already aware of possible mandatory bed rest or placebo effects of surgical interventions. He wrote "Several surgeons had a curious observation: elephantiasis improved in a spectacular manner after some major operation ... even if it has been performed on a different part of the body".

The temporary improvement which Handley in England achieved with the implantation of silk threads — an operation he described in 1908 and properly recanted two years later — was probably based on a placebo effect: silk threads don't exert lymphangiomotoric activity. The same holds true for the procedure recommended in 1917 by the French surgeon Walter, involving tissue implantation of rubber tubes.

In France, Griffon, in 1906 *(Fig. 3)*, published a case history of a fisherman who developed elephantiasis of the right leg after an injury inflicted by a fish bite followed by repeated attacks of erysipelas/lymphangitis. Griffon was unable to establish the cause of the edema. He wrote: "Our case can't be explained by a reduced venous circulation or by some disturbance of the nervous system ... The cause of elephantiasis is still unknown."

The implication of the "nervous system" in the etiology of edema is worth mentioning. At the turn of the 19th century, based on the view of the German Heidenhain, whereby lymph represented a secretion of the blood capillaries (so-called lymphogogues, such as extracts of strawberries and of crab muscle elevating lymph flow by triggering increased secretory activity), the opinion in France was deeply rooted that the nervous system played a decisive role in the origin of those edemas, in which nephropathies, phlebopathies and heart disease could be excluded and that a close relationship existed between




*3. French text by V. Griffon on elephantiasis of the legs.*

angioneurotic edema, urticaria and lymphedema. Indeed, these clinical pictures were regarded as different manifestations of the same neuropathy. Thus, angioneurotic edema and urticaria were regarded as acute, and lymphedema as a chronic form of a similar neuropathy. That is why Meige, in a paper published in 1898, designated the familial hereditary form of primary lymphedema as, "Dystrophie oedemateuse héréditaire," or "trophoedème." The word "trophoedème" meant neurogenic as pathways of the sympathetic nervous system were referred to as trophic fibers. Meige thought that the disease was triggered by an affection of those nervous centers which regulate the trophism of the subcutaneous tissue and that the trophic, vasomotor and secretory nervous centers were precisely coordinated with each other. Seven years later, Valabra in a paper entitled "Oedémes circonscripts aigus et chroniques sous la dependance du systéme nerveux" explained the etiology of lymphedema by a disturbance

of the innervation of the blood capillaries leading to increased lymph secretion.

Drinker and Field, 42 years after Heidenhain provided, in 1933, the proper explanation of how lymphogogues increased lymph flow: they elevate the permeability of the blood capillaries. Moreover, demonstrating that blockage of lymphatics of an experimental animal led to lymphedema, Drinker and Field established that lymphedema arises as a consequence of the inability of the lymph vascular system to drain away the lymphatic fluid load. In the same year, in France, Rouviere and Valette described that removal of the popliteal lymph node of the rabbit caused lymphedema which persists as long as there is no regeneration of the lymphatics. In spite of these studies, even in 1950, a 15 year old boy suffering from primary lymphedema was sent from France for treatment to Brunner, in Zurich, Switzerland with the following explanatory letter: "It's a matter of trophoedème without an arterial or venous obstacle. The etiology is not yet known but I used to have the impression that this condition which we see in these young people could be caused by some affairs with nervous troubles, difficulties with the parents, teachers, lack of contacts, etc.. I want to stress particularly that it is not a case of simulation, but a neurovegetative condition." This neurogenic theory has even prompted surgeons to perform sympathectomies in patients with lymphedema of the leg. As Brunner remarked in 1969, "no lymphedema has been improved and even much less has been healed by sympathectomy."

What conclusions can we draw from this short overview of the past?

First of all, it is remarkable how development of biologic knowledge runs in a crooked undulating line. Mascagni in the 18th century had a correct, deep insight into the etiology of lymphedema. His views were dismissed at the turn of the 19th century and replaced by a nebulous concept involving a defect of the nervous system. Starting with the third decade of the 20th century, a renaissance of the correct view has been reinitiated.

Concerning the treatment of lymphedema, it is ironic that the most important achievement of the past decades has been the rediscovery that the disorder can be successfully managed by a combination of physiotherapeutical measures. We are unable to compare the results one is able to achieve by CDP today with those obtained in the second half of the past century, because statistics are not available. But not only the highly respected dermatologist Kaposi commented on them favorably but even famed surgeons, such as Winiwarter and Esmarch, preferred them to extirpative operations.

Today there should be no "rivalry" between microsurgery and CDP. Nonetheless, the following facts should be taken into consideration:

No long-term prospective study exists which compares two homogenous groups, one treated by operation, the other by CDP. Although Nielubowicz and Olszewski described lympho-venous shunt operations in 1966, nowadays, (according to Olszewski), only 112 such operations are performed per annum worldwide.

The ingenious method of lymph vessel transplantation, introduced by Baumeister, is performed in 12 patients per annum. In our clinic approximately 1000 new patients are treated yearly by CDP.

Recently Sollano and her co-workers published a paper entitled "Volume outcome relationships in cardiovascular operations." They found a significant inverse relationship to exist between the outcomes and the volume of procedures performed. This fact should always be taken into consideration if top experts speak about their own results; these results cannot properly be extrapolated for general usage.

Concerning resective operations, which, according to Burnand, are indicated in 5 to 10% of cases of primary lymphedemas, Gloviczki has written in the Journal

"International Angiology" in 1999: "Prolonged hospitalization, poor wound healing, long surgical scars, sensory nerve loss, residual edema of the foot and ankle and poor cosmetic results can be significant problems and prevent offering such procedures short of a large and truly disabling lymphedema, not responding to medical measures."

From my perspective, if the necessary prerequisites are in existence, almost every lymphedema of a limb responds better to CDP than to resective surgery. Moreover, from the indications for these interventions mentioned by Gloviczki "impaired limb function, recurrent episodes of cellulitis and lymphangitis, intractable pain, lymphangiosarcoma and cosmesis," only angiosarcoma represents an absolute indication; intractable pain occurs only if lymphedema is caused by a malignant tumor or if plexopathy is present; episodes of cellulitis and lymphangitis can be sharply reduced and even eliminated by CDP.

Much has also been published about benzopyrones. They are interesting substances, but their therapeutic effect does not reach that of CDP; at best they may be used as an adjuvant treatment. As for Coumarin: it is, according to Loprinz and co-workers without beneficial effect in lymphedema.

Now I am going to say something which will not please those surgeons who over and over again propose modifications of breast cancer surgery, mainly in order to avoid or at least to reduce the frequency and the severity of secondary lymphedemas of the arm.

According to many, breast conservation surgery has approximately halved the frequency of secondary lymphedemas of the arm, but I could not find a paper concerning the frequency of lymphedemas arising in the "conserved breast"; we encounter them quite often. Lymphedema of the breast is no minor problem after irradiation; it is rather distressing that even an angiosarcoma can develop in the chronically lymphedematous breast. The treatment of breast lymphedema is also much more difficult than that of the arm. I have considerable doubt about the widely acclaimed "sentinel node" method as well. As long as the axillary lymphnodal status has therapeutic implications, the existence of false negative results is, to my way of thinking, extremely dangerous. Thus far, no long-term prospective randomized study exists which confirms that sentinel node biopsy actually reduces the incidence of arm lymphedema without detrimental effect concerning local recurrence of cancer and overall survival. I suspect that in the course of the 21st century, medical knowledge will triumph over solid organ cancers. This "victory" will automatically eradicate lymphedemas which arise after the treatment of malignancies and, of course, those which are caused by the blockage of lymphatics by cancer. As long as surgery has a major role in cancer treatment, the surgeon has to be regarded as an important factor concerning the development of lymphedema. For example, if a seroma arises after axillary lymphadenectomy, scar formation is more pronounced. Scar hinders the development of spontaneous lympho-lymphatic anastomoses, and the probability of lymphedema increases. I am convinced that progress in molecular biology, in genetic engineering, distrusted by many, who don't understand it, will in the not too distant future eliminate the primary lymphedemas caused by malformations and with improved public health that filariasis and tropical elephantiasis will also gradually disappear. On the other hand, I am less optimistic that lymphedema that develops in the final stage of deep vein insufficiency will become in the foreseeable future rarer. Whereas this form of lymphedema can be minimized or even prevented by lifelong compression treatment, at least 70% of patients refuse to wear the appropriate garments.

Iatrogenic lymphedema should no longer be caused by ignorance. For example:

1. The Swiss phlebologist Stahel reported in 1999 that he observed 10 patients with lymphedemas, in the course of one year, caused by 150 incisions for the stripping of varicose veins.
2. Unnecessary lymphadenectomies, as for example performed for inguinal node fibrosis, should be assiduously avoided.
3. The ventromedial bundle of peripheral lymphatics in the lower extremities should not be damaged by lipectomy and by meniscus operations on the knee.

As for diagnostic studies in lymphatic disorders. The important tool, isotope lymphography, (lymphoscintigraphy), has not as yet been standardized. There also remains the question, does liposuction damage the still functioning lymphatics in lymphedematous limbs? According to Kettering yes, according to Brorson no; according to the expert opinion of two leading specialists in nuclear medicine, Pecking and Tiedjen, neither Kettering's nor Brorson's results are acceptable, because Ketterings has injected the tracer into the skin and Brorson, after subcutaneous injection, has massaged the site of injection. The existing controversy concerning the injection site of the radiotracer should be resolved by the principles of "evidence-based medicine." Thus, an important remaining task for the immediate future is to reach a consensus concerning the optimal technique for isotope lymphography.

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